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PRESIDENTIAL ADDRESS*

OBSTETRICS AND GYNECOLOGY AS A UNITED SPECIALTY

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DURING the past twenty-five or more years, there have been steadily progressive changes in educational standards, and in methods of training in the specialties. For example, practically all except the youngest members of this Association were not able to have the advantages of present-day facilities for intensive training in obstetrics and gynecology, because, until comparatively recently, opportunities for this were so limited in number. Formerly, as most of us recall, one served his general internship as now, but training in obstetrics and gynecology was usually obtained by apprenticeship to a recognized and outstanding specialist. After more or less prolonged assistantship, one was allowed more responsibilities and wider latitude in his work, still under the close supervision of his preceptor. Hospital staff promotions followed gradually, and presently one became recognized, and rightly so, as a trained specialist.

Time has not lessened the value of this type of training in a specialty, and many men are following this course even now. More intensive methods have partly superseded this however, and to this end internships and residencies in the specialties are now being developed to a high degree of efficiency.

By the older method, young men were inevitably influenced by the personal views and medical activities of their preceptors. Lines of

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specialization were not sharply drawn. Gynecology was often a small portion of the work of some distinguished surgeon; another might find that gynecology constituted the major portion of his practice with obstetrics filling a minor place, or the reverse might be true. Younger men were prone, naturally, to follow the example of their masters, and thus the traditions were carried on. Many general surgeons whom we know and revere were trained in this manner to include gynecologic surgery in their work and nothing can detract from the brilliance of their performance of this in many instances.

During the past few years, however, multitudes of new discoveries in all fields of medicine have tended to limit the special activities of physicians within fairly sharply defined borders. On this and other accounts, we are obliged to face the facts of changing times and methods. All of us appreciate, as never before, the breadth and importance of the fields of obstetrics and gynecology, while their interrelationship becomes daily more apparent.

The subject chosen for presentation in this address was not singled out in a controversial spirit. Quite the contrary, it was selected for the express purpose of analyzing these definite transitions and trends in the teaching and practice of obstetrics and gynecology, which are becoming more and more widely established on this Continent. I refer particularly to the growing tendency to combine obstetrics and gynecology as a unified specialty in teaching institutions, in hospitals, and other practice. In Europe, this has been a customary and accepted combination for many years. In this country, however, one still hears a certain amount of persistent opposition to the logical suggestion that midwifery bears so close a relationship to diseases of women that they should be taught and practiced together.

By those not favoring this combination, childbearing seems to be regarded as a simple and normal function, which can be adequately supervised by any general practitioner. They grant that obstetrics is one of the most important branches of medicine, but decline to admit that its importance has developed obstetric specialists and the art of obstetric practice to an extent fully equal to that of any other major specialty. Gynecology is viewed by the same commentators as a mere branch of general surgery, free from any particular influence resulting from improvement in obstetric art, even though many gynecologic ailments are directly the result of poor obstetric care.

The more modern conception is that obstetrics with its multitudinous possibilities for trouble constitutes a major branch of medicine, and that diseases peculiar to women are inseparably associated with their childbearing functions. During recent years this idea has steadily gained more general acceptance on this Continent, although it still meets with sufficient antagonism to warrant a thoughtful analysis of the present situation, both pro and con.

TEACHING COMBINATIONS IN NORTH AMERICA

Accordingly, I inflicted another questionnaire on the Deans of the 75 four-year-medical schools approved by the American Medical Asso-

ciation in this country and Canada. Replies were received from 74 Deans, and I gratefully acknowledge my obligation to them for their generous cooperation in this study. So general a response clearly manifests their active interest in this moot question.

These replies show that the teaching of obstetrics and gynecology from a combined chair is carried out in 45 or approximately 60.8 per cent of the approved medical schools of North America. It develops further that 23 or 31 per cent have separate chairs for each, and it is significant that gynecology is combined with general surgery in only 5 or 6.7 per cent of our approved schools. In one school gynecology is divided between the surgical and the obstetric departments.

CURRENT OPINIONS FAVORING UNIFICATION

In contrast to these latter groups, the American Board of Obstetrics and Gynecology and the White House Conference definitely advocate the unification of obstetrics and gynecology for undergraduate and graduate teaching, and for practice.

Two years ago, Dr. Louis E. Phaneuf, in his presidential address before this Association, took for his subject "The Undergraduate Teaching of Gynecology." He discussed many of the points which I have in mind at this moment, but his theme dealt more with undergraduate education than with graduate training in the specialty. He expressed his firm conviction that the ideal way to teach gynecology to the undergraduate was from a combined chair of obstetrics and gynecology. He said that where this was not yet possible "the teacher of obstetrics should have fundamental training in gynecology as the teacher of gynecology should have in obstetrics, if the best results are to be obtained," and he further stated "For purposes of teaching and giving the patient the best care, the department of gynecology in large hospitals should be separated from general surgery and should function as a unit or as a part of a woman's clinic." This is sound logic, and applies equally well to the teaching and training of resident house officers and other graduate students.

Six years ago, Dr. Walter T. Dannreuther chose as the subject for his presidential address before this Association "The Qualifications of the Specialist." He called attention to the fact that the medical profession has been afflicted with numberless irresponsible self-styled specialists. He said, "The term 'specialist' implies that the individual so designated has had superior training and has assimilated knowledge from a multitude of opportunities, and the public is just beginning to display an interest in the qualifications he really possesses and to question his authority for so classifying himself." This summarizes admirably the reasons which caused the twelve major specialties in medicine to organize certifying Boards. As you well know, these Boards investigate carefully the special training and practice of applicants for certification as specialists, and then conduct rigid examinations to ascertain the extent of their special proficiency before granting certificates. As Dr. Dannreuther said, "The chief purposes of our Board (like the others) are not restrictive but educational: to encourage and induce potential

specialists in obstetrics and gynecology to prepare themselves thoroughly, to persuade medical schools and hospitals to provide adequate facilities for special training, and to put the stamp of approval on qualified specialists." He further said, "The departmental integration and fusion of obstetrics and gynecology is not only desirable but highly essential, because the skillful practice of one is dependent upon a thorough knowledge of the other. It must be conceded that the large Frauenkliniks abroad are far better equipped to produce specialists than our own institutions, although the available clinical material is no greater."

From its beginning the American Board of Obstetrics and Gynecology has insisted that a fundamentally thorough knowledge of both branches is essential, regardless of whether a physician elects to practice one or the other, or both. Therefore, the examinations include both subjects, with especial emphasis on this interrelationship.

In this connection it would have been of interest, had it been possible, to inquire into the arrangements in the many general hospitals of this Continent having obstetric and gynecologic departments, because it is in them that many men receive their graduate training in the specialty. Nevertheless, it is likely that the methods provided for undergraduate instruction in the medical schools are a fair index of graduate training facilities, and of practice in general. Each of these schools has its affiliated hospital, and nonteaching hospitals are likely to emulate the example of the others.

COMMENTS ELICITED BY QUESTIONNAIRE

My questionnaire and the comments it elicited developed many interesting facts.

There seems to be no serious argument over the fact that the childbearing function and diseases of women overlap and interlock so closely that there can be no sharp line of demarcation between them. However, in an attempt to divorce the two in one of these teaching institutions, patients with pelvic disorders are still claimed by the surgical division unless their illness is clearly the result of some obstetric experience or calamity. In the latter event they are conceded to the obstetric and gynecologic division, considered in this particular institution as being "combined." Thus a retrodisplacement of the uterus with symptoms in a nulligravida, which is seldom a surgical problem, is viewed as a case for the general surgeon, whereas a similar condition following pregnancy is assigned to the obstetrician-gynecologist.

In still another important teaching institution, in which it is strongly asserted that gynecology is properly a branch of general surgery, assignment of cases is based upon the rule that all women with pelvic disorders who have not previously been patients in the obstetric division are to be admitted to the surgical-gynecologic service. Only if they have ever been patients on the obstetric service may they return to this department for gynecologic treatment. Thus, a woman with an ectopic pregnancy is not an obstetric case unless previously she had been a patient in the obstetrical department. Both services receive and treat cases of ectopic pregnancy according to this ruling. Indeed, they go even

further than this in this hospital. A patient with a fibromyoma or an ovarian cyst applying for admission is likewise questioned as to previous admissions. If she has had a baby or even an abortion treated there at some previous time her tumor becomes mysteriously related to obstetrics, and she is admitted to and operated upon in the maternity division.

At this same institution, the interns, assistant residents, and residents in gynecology may serve periods of time varying from one to four or five years without ever seeing an obstetric case, without any personal insight into the later effects of some of their pelvic surgery when pregnancy occurs, and without any arrangement whereby they may routinely rotate or have exchange services with men from the obstetric division, if they should wish thus to broaden their knowledge.

Is it necessary to reiterate at this point, that both in teaching and in practice an attempt to create a dividing line between obstetrics and gynecology is impossible, and at times becomes almost ridiculous? Furthermore, gynecology does not bear an inseparable and constant relationship to surgery. In a recent publication I took occasion to say, "Gynecology . . . . includes not only local or genital diseases of women, but general and associated glandular dysfunctions. By far the greatest bulk of gynecologic practice is nonoperative, and this, too, should serve . . . . to controvert the suggestion that this specialty should be considered a subdivision or branch of general surgery. Office treatments of ambulatory patients predominate greatly in numbers and probably in variety of purposes over hospital admissions and major operations for gynecologic disorders."

OPPOSITION TO UNIFICATION

Having expressed some very definite opinions as to the propriety of combining obstetrics and gynecology, it is proper to consider the other side of the question and to examine the arguments offered against such a union.

The first of these is that "The obstetrician-gynecologist cannot cope with emergencies of abdominal surgery as efficiently as can the general surgeon. He must be trained in and practice general surgery in order to be a safe gynecologist in the abdominal cavity." Some of the emergencies mentioned were intestinal obstruction and tumor growths of the gastrointestinal tract, as well as cholecystitis and cholelithiasis. But does this doubt apply to the properly trained obstetrician-gynecologist? It is agreed that a competent gynecologist must have had good training in abdominal surgery even though these emergencies are distinctly a minor part of his work. It should also be remembered that the interrelationship of obstetric matters is by no means a minor, but rather is a constant, part of his gynecologic work, so that training in this is of more importance than an intensive one in general surgery.

It was interesting to note what constituted "adequate training in gynecology" in the opinion of this particular critic, whose own department is a subdivision of general surgery in his school of medicine. He has a small corps of interns and assistant residents, headed by a chief

resident. While his department is rated as a subdivision of surgery, his men are appointed directly to this gynecologic subdivision, do not rotate through or serve in the general surgical department, and receive their entire training in the gynecologic operating rooms and wards. Their training under his direction is no broader or more inclusive, or better suited to fit them for the general surgical emergencies mentioned, than that of any similar but truly gynecologic service combined with obstetrics. Moreover, there is an entire lack of obstetric experience or training for these men, and I question the likelihood of their seeing any more general surgical emergencies than are met in any average obstetric-gynecologic service.

Let us continue with the quotation. Amplifying his argument, this same authority said, "For example, suppose a gynecologist were to operate for a large fibromyoma of the uterus, and found a gall bladder full of stones." Insisting that such a man's operative ability must perforce be limited, he demanded to know what this operator would do. Would he remove the uterus, and meanwhile summon a surgeon to stand by to remove the gall bladder, or would he be so remiss toward the patient as to remove only the uterus and leave the gall bladder, because of his lack of general surgical ability? Apparently in the vehemence of his argument it did not occur to him to question the soundness of judgment of any surgeon who would subject his patient to a hysterectomy for fibroids, at the same time throwing in a cholecystectomy for good measure.

Another comment makes one ask what possible benefit in the way of general surgical training or experience can follow the subordination of gynecology as a division of general surgery in an institution from which the Dean writes as follows: "Female urology forms part of the work of our Department of Gynecology. Administratively the Department of Gynecology is considered to be a sub-department of Surgery. As a matter of fact it is largely autonomous. I doubt if the Professor of Surgery ever sets foot in the gynecologic operating suite."

Still another objection offered to the combination of obstetrics and gynecology is that "men trained in obstetrics and gynecology sooner or later drift into the practice of one or the other, seldom continuing with both. The majority, as they grow older, major in gynecology, dropping their obstetric work because of its arduous nature." I do not believe that this is true of the obstetrician-gynecologists trained by modern methods in the combined specialty. Even if it is so, they are better gynecologists and better teachers for having had their broad fundamental training and experience in these closely related branches.

A third argument was, "A man cannot operate on scheduled cases in the morning if he has been up all night with an obstetric case." In a recent paper, Stander dismissed this adequately by the comment that "all doctors specializing as obstetricians and gynecologists, have connections with hospitals, most of them first class, thanks to the efforts of the American College of Surgeons and the American Medical Association. Good hospitals with trained resident staffs are decreasing the necessity of all-night vigils with every patient in labor."

It was startling to have the Dean of another of these five schools write, "I think that we need more conservative obstetrics and think that this cannot be obtained by combining obstetrics and gynecology."

The Dean of the one school in which gynecology is divided between the surgical and the obstetric departments says, "Possibly the most important reason why gynecology is retained in part by the surgical service is the fact that it is felt that the general surgeon will continue to do the major portion of operative obstetrics for many years to come, if not indefinitely."

If there are other reasons against a combination of obstetrics and gynecology as a united specialty, they have not been given me. The relative worth of such arguments should be obvious.

EFFECTS OF UNIFICATION

Let us clearly understand what is meant by the unification of obstetrics and gynecology. It does not mean that one trained in the specialty of obstetrics and gynecology must practice both, but first that he will be better qualified in either branch because of his knowledge of the other. The time will soon come, in all probability, when all those who have been thus broadly trained will practice not merely one or the other, but both, because of the fascinatingly engrossing interrelationship of the two. It does not mean that any one can fairly contend that the general surgeon is unqualified or unfitted to do female pelvic surgery. The results of numerous brilliant surgeons, many of them Fellows of this Association now and in the past, refute such an implication or conclusion.

It does mean that there is a growing appreciation that the teaching of undergraduate medical students, and the training of graduate students, are best accomplished when obstetrics and gynecology are correlated by being departmentally united. Properly to teach the younger men who will succeed us, those giving the instruction should have a background of wide experience in both branches, and preferably should practice what they teach. Needless to say, both obstetrics and gynecology are non-elective subjects for undergraduate students, being "required" subjects in all American schools. The combination also means that patients requiring the solution of either gynecologic or obstetric problems will receive the greatest benefit if they are in the hands of men having this breadth of background.

Fundamentally and basically, therefore, the problem becomes one of training. Those who have had adequate education in the combined specialty should be similarly training the potential specialists. They can best do their teaching of the younger men, while these are serving as interns, assistant residents, and residents on combined hospital services. In institutions with medical school affiliations, these same trained men should be teaching obstetrics and gynecology and the elements of their interrelationship to the undergraduate.

Let us see how this applies in the three different groups of schools. In the hospitals of all of the 45 schools having combined chairs the resi-

dents, assistant residents, and interns are given a well-rounded and balanced service in the combined specialty.

In contrast to this, in the 23 having separate chairs, residents alternate or rotate through both services in only 4, and through obstetrics, gynecology, and surgery in only 4 more. There is a partial rotation in 1 other. At 13 of these institutions the residents serve either in gynecology or in obstetrics, but not in both, so that their training here is presumably deficient in one or the other.

The assistant residents fare about the same, as is shown in Table I, but internes are required more generally to serve in both departments.

In those in which the chair of gynecology is combined with that of surgery the residents rotate between surgery and gynecology in only 1, and between surgery, gynecology, and obstetrics in only 1 other. The assistant residents and interns have generally similar facilities, the importance of related obstetric training apparently being minimized.

Graduate training in obstetrics and gynecology presents two distinct aspects. There are many men who do not intend actually to specialize in this work but whose interest impels them to seek something more than the limited experience derived from an average rotating internship. Still others may have been in practice a few years, and wish to improve themselves in special work. One problem therefore concerns itself with the matter of providing graduate training for limited periods of time for these men. The other is that of providing training facilities for those planning to specialize in obstetrics and gynecology.

Many hospitals offer special internships for men who have completed a general rotating internship there or elsewhere. These services are usually for one year, and in many of these four men are appointed. This provides ideal training for a man who does not intend to specialize, but who plans to engage in general practice with special attention to obstetrics and gynecology. It is also a good foundation for those who propose to work up more slowly to specialization through the medium of dispensary and assistant staff attending positions in a department of obstetrics and gynecology of some general hospital.

If these same institutions could arrange assistant internships, externships, or voluntary assistantships for periods of three or four months, perhaps with a registration fee, they would probably be crowded with applicants. Such positions would be in great demand among general practitioners anxious to improve their knowledge and to bring themselves up to date from time to time. Unfortunately such opportunities are not generally available.

Assistant residencies, and residencies of one year each, as now provided, are usually obtained by promotion from the internships. For example, two of four interns are chosen to become the assistant residents, and one of these in turn is appointed to the residency for the ensuing year. At the majority of hospitals with such services, salaries as well as maintenance are paid to some of these men.

Certain hospitals in this country do not provide so complete a course of training, but absorb the assistant residents or even the interns who fail to obtain the promotion, or who wish to acquire other viewpoints by

going elsewhere. For example, many general and some special hospitals with assistant residencies and residencies prefer to have these men come to them from other clinics after their special internship of one year.

Thus, a variety of facilities for special training in obstetrics and gynecology are available in this country. Recently, a Committee on Graduate Education of the American Board of Obstetrics and Gynecology undertook to survey and list the institutions having services such as these. Its findings were published in the *American Journal of Obstetrics and Gynecology*,[5] in April, 1936, and should be consulted by those seeking such appointments.

To return to my original theme, I agree emphatically with Dr. Phaneuf that undergraduate teaching of obstetrics and gynecology should be from a combined chair. I reiterate the suggestion that graduate training is best given in a combined hospital service, and that the only compromise with this can be where provision is made for rotation of interns, resident assistants, and junior staff assistants between the two services. Even this is not as satisfactory as to give them their practical training under one head or director who is able from personal experience to correlate the teaching in the two branches. I subscribe wholeheartedly to the viewpoint of the American Board of Obstetrics and Gynecology that even those men who wish to practice or teach only one of these two branches are not adequately qualified to do so without a thorough training and experience in the fundamentals of both. I repeat that modern gynecology is not being well taught when its precepts come from a chair of general surgery, with the chair of obstetrics entirely alienated from the subject. The teaching of obstetrics and of gynecology suffers when their chairs are separated.

CHANGES IN TEACHING METHODS

If these concepts which I have presented are valid, how then may the situation be corrected in those institutions naturally resistant to revision of their longstanding traditions, yet inclined to conform with the current trends and to improve their methods of undergraduate as well as graduate teaching of our specialty?

I have no desire to appear in the role, alliteratively described by the late Barton Cooke Hirst, as that of a "nonteacher trying to teach teachers how to teach." It is quite possible, however, to acquire a viewpoint unaffected by local conditions or political expediencies, and to envision the matter entirely from the standpoint of results. Moreover, what is now being said about teaching institutions applies equally well to hospitals without teaching affiliations. The latter predominate numerically, and render an important service to the women of this country, incidentally providing training for many future specialists and practitioners in obstetrics and gynecology. I have ventured, therefore, to formulate certain ideas and to offer certain suggestions on this account, but not on this account alone.

In the position with which I have been honored for several years, namely that of Secretary of the American Board of Obstetrics and Gynecology, I have received an extraordinary number of communications on

TABLE I.—GYNECOLOGY AND OBSTETRICS IN THE
(FOUR-YEAR
TOTAL INQUIRIES
ANALYSIS OF

CHAIRS	TOTAL	PER CENT	DURATION OF COMBINATION	PRESENT ARRANGEMENT SATISFACTORY	ARRANGEMENT UNSATISFACTORY	CONTEMPLATING CHANGES
Gynecology and obstetrics combined	45	60.8	Within last 10 yr.: 16 Within last 20 yr.: 7 Longer than 20 yr.: 22	42 (No answer 2)	1	0
Gynecology and and obstetrics separate	23	31.0		15	8	Combination with obst. planned: 5 Combination with obst. under discussion: 1 Opinions divided: 1 No plans: 1
Gynecology and surgery combined	5	6.7	Within last 10 yr.: 1 Longer than 20 yr.: 2 No answer: 2	5	0	0
Gynecology combined partly with surgery, and partly with obstetrics	1	1.3		1		
Total	74			65	9	8

this very subject. The Deans of two medical schools, and the secretaries of a number of hospital staffs have addressed the Board to the effect that they have taken cognizance of the Board's demands that candidates for certification must have a specified minimum training in both obstetrics and gynecology. They have recognized that the logical way to provide this is by an integration of these departments. In some instances, this requirement of the Board may have had only a minor influence upon their decision, their altered viewpoint being initiated by the very force of the plan's own logic.

From these conferences a simple plan of procedure seems naturally to have evolved itself. It is not an official suggestion of the Board, because the Board is merely an examining body and has never undertaken

MEDICAL SCHOOLS OF THE UNITED STATES AND CANADA

"GRADE A" SCHOOLS)

75—REPLIES 74

TEACHING PLANS

DEPARTMENT HEADS			HOUSE-STAFF TRAINING IN OBSTETRICS-GYNECOLOGY								
FULL TIME	PART TIME	CLINICAL	SERVICE	OBST.-GYN. COMBINED OR HAVING INTER-ROTATION	OBST.-GYN. SEPARATED: NO INTER-ROTATION	OBST.-GYN. SEPARATED: PARTIAL INTER-ROTATION	OBST.-GYN. AND SURGERY INTER-ROTATION	GYN. SURGERY INTER-ROTATION WITHOUT OBST.	NO ANSWER	UNDERGRADUATE TEACHING OBSTETRICS-GYNECOLOGY REQUIRED SUBJECTS
10	20	14	Resident	45						45
Obst. part time & gyn. "clinical" 1			Asst. resident	45						
			Interne	45						
1	8	7	Resident	4	13	1		4	1	23
Obst. part time, gyn. clinical: 5 Obst. full time, gyn. part time: 1 Obst. full time, gyn. clinical: 1			Asst. resident	3	12	1		3	4	
			Interne	11	3			7	2	
0	2	3	Resident		2		1	1	1	5
			Asst. resident				2	3		
			Interne		1		1	3		
1 (Modified)			Resident		1					1
			Asst. resident		1					
			Interne				1			
12	30	24	Resident	49	16	1	1	5	2	74
			Asst. resident	48	13	1	2	6	4	
Mixed 8			Interne	56	4		1	10	2	

to interfere with or direct the policies of any group or institution. The Board does no more than establish certain minimum standards of education and training as a basis for admission to its examinations.

The Dean of one school of medicine wrote some time ago that the trustees wished to reorganize their departments of obstetrics and gynecology, combining the chairs into one, and asked if we had any suggestions to make as to how the new department should be organized and conducted. He said in effect that he dreaded the repercussions, and the disappointments of some who would be adversely affected by the change, but that they were all convinced of the wisdom of the move. His letter came at about the same time that one of a similar nature was received from another Dean of a school in which one chair had been vacated by

the death of the incumbent. During the same period others were received which related to the reorganization and combination of departments in three hospitals without teaching or medical school affiliations. After considerable correspondence, and even some personal conferences, certain facts developed. At the outset, it was clear that in all such institutions, a general upheaval is undesirable. Those men who have supported them faithfully for years should not be slighted, but obviously should be retained and absorbed wherever possible in any such reorganization.

The principal difficulty seemed to be that of the choice of a director for any new department of obstetrics and gynecology. In one instance the importation of a man from elsewhere solved their problem; in another, they appointed the senior man who limited his work almost entirely to gynecology, although he had had excellent training in obstetrics; in the institution in which a vacancy was created by death, the occupant of the other chair was given the new combined post; in still another, the younger of the two men was selected solely because he had had a broader training and was better equipped.

Under these heads, holding the newly combined chair or staff position, it was suggested that a professorship, or senior staff position, in obstetrics and similarly one in gynecology be created, subordinate to the head of the combined department, with respective groups of associates and assistants being given lesser positions so that the whole formed a strong pyramid with a broad base. No dismissals were necessary, no demotions were required, and no restrictions of duties or privileges needed to be imposed. Indeed, the activities of all department members, previously restricted by the limits of their department, were immediately broadened in scope and interest, according to an individual's ability. A new administrative head of the combined department having been appointed, his greatest responsibility became that of coordinating the work of the two groups as rapidly as possible. Such a reorganization must necessarily be developed gradually. In certain instances it involved additional graduate training for some of the department members themselves. A gradual fusion with the least possible, but occasionally necessary, elimination or restraint of those unable to adapt themselves was infinitely wiser than an abrupt and sweeping change in any of these institutions.

The most important reform of all was that whereby the resident house officers and students were compelled to weave their activities into the work of the two groups without any imaginary or arbitrary dividing line, so that instruction and training in gynecology and obstetrics were integrated by clinical precept and management of cases.

TYPES OF PROFESSORSHIPS

In the questionnaire, due notice was taken of the material or financial side of this question as this is of considerable importance to all schools which must function usually with less than adequate endowments. Reference to the table shows that the part-time professorship plan predominates in North American schools.

Full-time professorships are those under which the incumbent is paid a salary and gives his entire time to the position he holds; part-time professors receive a lesser salary as reimbursement for their school activities but are allowed the privilege of a limited amount of consultation and other "private" work. The professorship designated here as "clinical" is that under which the school pays no salary, and the incumbent's entire livelihood comes from his clinical or "private" practice.

The first of these is a fairly recent innovation about which certain objections have been raised. It has been said that the full-time professor, by being cloistered, is forced out of touch and out of sympathy with the general medical profession. Local jealousies seem prone to develop and the school's hospital and special services suffer not only from nonsupport but often from active opposition from the local profession. This is especially true in those places where private patients are admitted to the care of a full-time specialist, the institution taking the patient's medical fee. The profession objects that such an institution is actively competing in the practice of medicine with the physicians of that community.

Capable men who take these positions must make considerable financial sacrifices because their earning powers in ordinary private practice are usually considerably more than the salaries which their institutions can afford to pay them. Consequently, such men are relatively few in number, not easily found, and their institutions impose a constant hardship on them at the same time that they expect and receive the intense loyalty of these men.

The third or "clinical" type of professorship is one which is often dictated by necessity. An outstanding man in a school's community, supporting himself entirely by his clinical practice, may have been chosen outright or may have worked up to the professorship through promotions. His compensation for his school work is the prestige of the position, and the consultation work which may come later from the students he has taught and trained. His personal interests usually come first, because he is no more than human, and his school work is often secondary to the demands of his practice. In the selection of such men the school is ordinarily limited in choice to practitioners in the school's immediate vicinity.

The part-time professorship seems to be an ideal compromise between these other two plans. This survey demonstrates that it is the most widely favored plan at the present time. From the standpoint of the school it is more economical than the full-time professorship. It is less restrictive and more broadening in opportunities for the individual, and generally more inviting to any capable man than either of the others. Under this plan, men may be attracted to come to a school from elsewhere if that is desired, or local men find it possible to discontinue the routine and relatively unimportant parts of their private work in order to give more time to the school.

Incidentally it may be remarked that under either the full-time or part-time plan, the unification of the departments of obstetrics and

gynecology is, obviously, an economical move so far as salaries and other administrative expenses are concerned.

GENERAL

This transition which has been discussed is still going on. In those places where it is complete, the general surgeon no longer fears or finds that the gynecologist wishes to invade his domain, obviously with less skill than that possessed by the general surgeon. In fact, indiscreet excursions into general surgery by the gynecologist constitute another valid reason against the policy of including gynecology in the department of general surgery. Obstetrics and gynecology is a field of sufficient breadth to test the skill, engross the entire interest, and require the full attention of any one man. Working in such a broad specialty he will have no inclination or time, even in the unlikely event that he possesses the ability, to invade the field of general surgery.

Furthermore, in the course of due time, it should be found that the obstetrician-gynecologist will have less and less occasion to object that the general surgeon in his institution continues to undertake female pelvic surgery. Comparison of results between the two departments should take care of this situation, and if they fail to prove his advantage something is wrong with the gynecologist.

Criticism, to justify itself, should be constructive. What then shall be the constructive thought which should accompany the criticism in this address?

It is obvious that specialization in any field of medicine can be improved by higher educational standards and better training facilities, to the end that our sick populace will benefit when the help of a specialist is needed, whatever the nature of his affiliations. For the protection of the public, if there are to be specialists in the several branches of medicine, let us make certain that they are well trained and not merely self-styled ones. What this country needs is not more but better specialists. Adequate training through the medium of hospital residencies or of staff assistantships for prolonged periods of time is the only reasonable solution to this.

Our particular problem in this march of progress is specialization in obstetrics and gynecology. I am convinced that our answer is to be found in the unification of obstetrics and gynecology into one specialty for the purposes of teaching of students, clinical training of one's assistants, and actual practice for oneself, all to the immediate advantage of the patients for whom we are caring.

1010 HIGHLAND BUILDING

STUDIES ON THE ENDOMETRIUM IN ASSOCIATION WITH THE NORMAL MENSTRUAL CYCLE, WITH OVARIAN DYSFUNCTIONS AND CANCER OF THE UTERUS*†

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A WORKABLE classification of the endometrial findings in the normal menstrual cycle has been outlined in previous papers.[1-3] The classification was based on a study of 241 endometrial specimens removed either at dilatation and curettage or by means of the Randall uterine biopsy instrument.

CLASSIFICATION OF OVARIAN DYSFUNCTION

A fairly simple clinical classification of the various types of ovarian dysfunctions also has been adopted. In general, they are divided into two large groups: the "primary ovarian dysfunctions" and the "secondary ovarian dysfunctions." In the former group failure is primary in the ovary itself. In this group, one is confronted not only with the problem of menstrual irregularity, and often sterility, but also with a train of symptoms associated with true ovarian failure. There is no evidence in this group of pituitary disturbances such as abnormal fat metabolism, abnormal water metabolism or lowered basal metabolic rate.

The second large group includes the primary pituitary and thyroid failures in which ovarian failure is, of course, a secondary phenomenon. In this group evidence of disturbances of fat metabolism as well as of water metabolism and lowered basal metabolic rate often are found. This, roughly of course, constitutes the clinical classification.

From the histologic standpoint the evidence of ovarian dysfunction, however, is the same in both groups since the endometrial pattern changes with ovarian function regardless of whether the cause of its abnormal function comes from within or from without the ovary. It becomes apparent, therefore, that one cannot classify these dysfunctions on the basis of the histology of the endometrium only but histologic examination does form a part of the armamentarium in arriving at a rational diagnosis. Biopsy of the endometrium, with study of its histologic characteristics, is of greatest value in recognizing a subdivision of these ovarian dysfunctions into the groups of partial or complete ovarian failure, regardless of whether the failure is primary or secondary. Since the regenerative phenomenon seen in the endometrium

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depends on the ovarian hormones for its stimulus, any degree of failure of this stimulus, or stimuli, can be recognized. The proliferative phases of the endometrial cycle, as has been seen, are dependent on the follicular hormone, and the differentiative phases depend on the normal activity of the luteal hormone. If either of the hormones is absent or deficient, then the regenerative phases likewise will be absent or deficient. Further, the prolonged activity of one or the other hormone will result in prolongation of the phase controlled by this hormone.

On the basis of this histologic and physiologic explanation I have proposed the term "persistent phases of the cycle" which at once denotes the deficiency in ovarian function which is manifested by the endometrial change. The interpretations have been consistent to the degree that often it is possible to predict the type of clinical syndrome associated with a given histologic pattern.

As examples of the persistent phases mentioned above, which are associated with ovarian dysfunction, a few of the representative tissues are here presented.

Persistent Early Proliferative Phase.—The word "persistent" used in this classification denotes the histologic state of the endometrium and at the same time postulates abnormal function of the ovary. For example, an ovary that is deficient in production of luteal hormone and that is to some degree deficient in follicular production will express these changes by a lack of development (or regeneration) of the endometrium, and the endometrium, therefore, will remain in a state of persistent proliferation. Such an endometrium is not hypertrophied or hyperplastic in any sense—in fact, often such an endometrium will appear microscopically the same as the endometrium usually seen in the first seven days of the normal cycle. It is obvious, therefore, that a pathologic diagnosis need not be made but rather a report of the degree of ovarian failure can be given. In addition to histologic accuracy, such a report is of more diagnostic value to the clinician than is a pathologic diagnosis. The specimen shown here (Fig. 1) represents an endometrium removed on the twentieth day of an abnormal cycle. This specimen, if it had been taken on the twentieth day from a patient whose cycle was normal, should give evidence of differentiation, which is a normal corpus luteum effect. However, histologic study discloses that the endometrium is arrested in the proliferative phase. The patient was a bleeder who previously had been given theelin; incidentally this produced more, rather than less, bleeding. It becomes clear that this patient did not lack theelin, which is the proliferator of the endometrium, but rather the deficiency is one of stimulation by corpus luteum. The treatment indicated, therefore, is one which is designated to bring about stimulation of the corpus luteum. This same type of endometrium may also be seen occasionally in cases of amenorrhea; nevertheless, the basic disturbance in the ovary is the same. The problem of the exact cause of bleeding obviously still baffles students of this subject.

Persistent Late Proliferative Phase.—The principles outlined in the preceding paragraph apply in examination of specimens in this phase. Again the endometrium reflects the state of ovarian function and the difference herein is one of degree rather than of kind. A persistent late proliferative phase found on examination of a specimen of endometrium removed in the last part of a regular, or of an irregular, cycle denotes merely that a full proliferative or follicular effect has been exerted on the regenerating endometrium. The only ovarian deficiency evident in this phase, therefore, is in production of the luteal hormone. Again, the change is not hyperplasia but arrest of the regenerative phenomenon. Patients whose tissues can be classified in this group, interestingly enough include the largest number of bleeders, and, therefore, constitute clinically one of the most important groups of patients. The treatment likewise is not by administration of theelin but of a luteinizing hormone. The endometrium usually will have characteristics almost identical with

those of a normal late proliferative phase of a normal cycle. The glands are somewhat dilated but they are straight, tubular glands; approximately six such glands are found per low power field. The gross thickness of the endometrium usually is not more than 2+ mm. Fig. 2 represents a state of persistent late proliferation in an endometrium removed on the twenty-third day of the cycle. This patient complained of hypomenorrhea but her cycle was fairly regular. Her primary complaint was sterility although patients of this group usually complain of menorrhagia. This patient's urinary estrin content was normal but pregnandiol was completely absent from a twenty-four-hour specimen of her urine. This indicates complete absence of the luteinizing hormone.

Persistent Early Differentiative Phase.—The types of abnormal ovarian function associated with tissue classified in this group are interesting. A state of persistent early differentiation denotes, as would be expected, partial failure of corpus luteum and again the endometrium appears like that seen in the third week of the normal cycle, in which there has been a partial but not a complete luteal effect on the

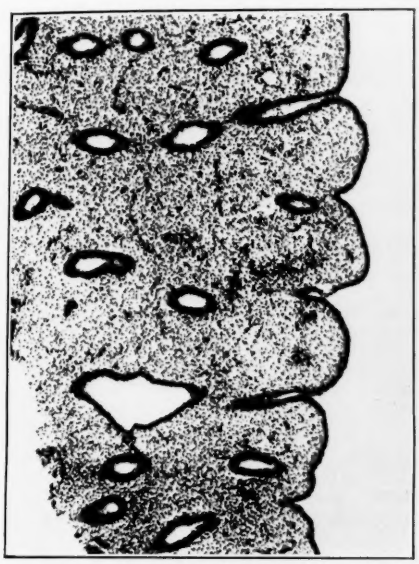

Fig. 1.

Fig. 2.

Fig. 1.—Persistent early proliferative phase of menstrual cycle. Glands identical with those seen in the first phase of the normal cycle; they are small, straight, tubular glands lined with low epithelium. This endometrium does not differ from normal endometrium in any respect except that it was removed in the last part of a cycle and it contains an occasional cyst. No actual increase in the total number of glandular elements (although previously called hypertrophied or hyperplastic endometrium). Average thickness of endometrium, 1 mm. Hematoxylin and eosin (×50).

Fig. 2.—Persistent late proliferative phase of the menstrual cycle. Average thickness of endometrium approximately 2 mm. Glands nearly identical with those found in same phase of cycle in a normal endometrium in the late proliferative phase. Average number of longitudinal glands per low power field is six. Hematoxylin and eosin (×50).

endometrium. Bleeding is less among the patients corresponding with endometrium of this group than among those mentioned in the preceding paragraph. Differentiation may, therefore, to some degree prevent the bleeding. One of the common findings in this group is sterility and there are a few cases of hypomenorrhea. The histologic characteristics are not greatly different from those of the normal early differentiative phase. The number of glands is essentially the same. In this group the glands are more convoluted and the proliferative epithelium changes, under partial corpus luteum effect, to a more columnar differentiative epithelium. The gross thickness of the endometrium is approximately 3 mm. The specimen illustrated

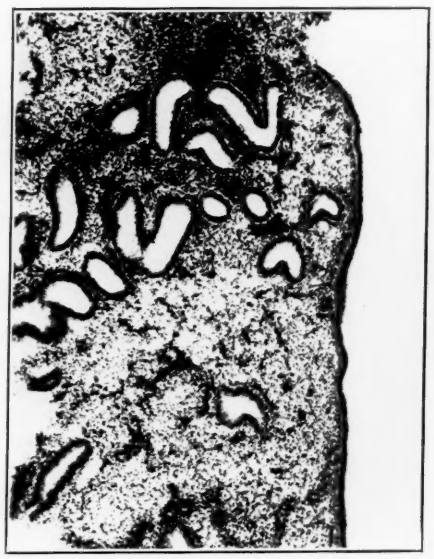

Fig. 3.

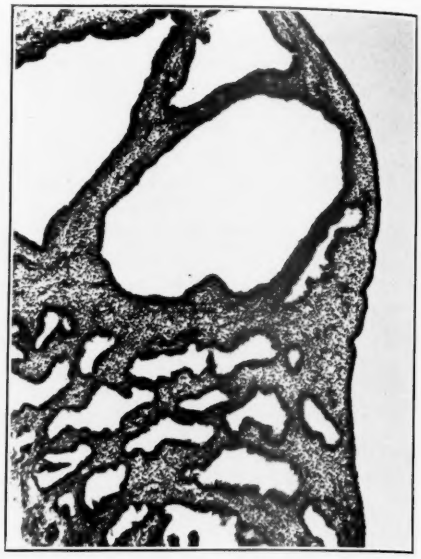

Fig. 4.

Fig. 3.—Persistent early differentiative phase of menstrual cycle. The longitudinal glands are characteristic of the early differentiative phase. The glands are lined by columnar epithelium and have convolutions which are normal for the early differentiative phase, that is, the fourteenth to twenty-first day of the cycle. The average number of longitudinal glands per low power field is six to seven. Endometrium does not differ greatly from the normal yet was taken at the time of the cycle when differentiation should be complete. Some effect of the corpus luteum hormone is evident in the endometrium. However, absence of complete differentiation indicates a partial failure. Hematoxylin and eosin (×50).

Fig. 4.—Persistent late differentiative phase of the menstrual cycle in a cystic endometrium. Complete differentiation is evident. There are six to seven longitudinal glands to the low power field but differentiation is complete. The abnormal feature is the presence of cystic areas existing in an endometrium which histologically gives evidence of the nearly complete effect of the hormone of the corpus luteum. Hematoxylin and eosin (×50).

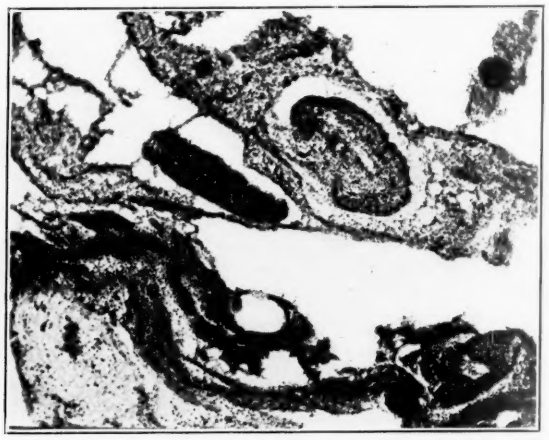

Fig. 5.—True atrophic endometrium result of dilatation and curettage or biopsy. Note small islands of epithelial cells with loose stroma. Hematoxylin and eosin (×50).

(Fig. 3) was removed from a patient who complained of sterility and who, following stimulation by corpus luteum, became pregnant.

Persistent Late Differentiative Phase.—When the degree of ovarian failure is small, that is, when there is nearly a complete luteinizing effect on the endometrium, the histology of the endometrium is also only slightly altered. Differentiation is complete, or nearly so, but clinically there may be some slight abnormality in the menstrual cycle. However, most of the patients menstruate regularly and complain of either sterility or of some symptom suggestive of ovarian failure. Such an endometrium as that under consideration usually will contain six to seven longitudinal glands per low power field. In longitudinal section these glands appear as a sectioned seashell. The glands are lined by columnar, differentiated epithelium. Cases of this sort are favorable to treat because only slight stimulation often will correct the dysfunction. Cystic changes often are seen in this type of endometrium and constitute a very definite abnormal finding (Fig. 4).

Atrophic Endometrium.—The term "atrophic endometrium," like "hypertrophic endometrium," has been rather loosely used. It has been applied to menopausal as well as to postmenopausal endometrium; however, observations made in this study would indicate that the term "true atrophic endometrium" would be more applicable to that type of case in which complete and rather sudden ovarian failure has occurred. Following sudden failure (either spontaneous or artificial failure, that is, surgical removal of the ovarian tissue), there occurs a lack of both the follicular and corpus luteum stimulus to endometrial regeneration, and hence, true atrophy occurs. The gradual failure of the ovaries incident to the climacteric is usually associated with cystic formation as stated above. However, as stated, sudden withdrawal or failure of ovarian tissue is accompanied by true atrophy. The remaining endometrium consists of a single layer of epithelium overlying a loose stroma. This is typical of true atrophic endometrium, biopsy of which or even vigorous curettage will result in securing only small amounts of endometrial tissue. However, a diagnosis can be made on the presence of small islands of epithelial cells lying usually in the loose stroma described above. Fig. 5 illustrates true atrophic endometrium removed from a patient twenty-nine years of age who presented amenorrhea with sudden onset twelve months before admission.

THE ENDOMETRIUM ASSOCIATED WITH CANCER

The foregoing studies have had to do primarily with endometrial histology in association with the normal cycle as well as with the endometrial findings in association with ovarian dysfunction. I am of the opinion that the classification outlined is more useful than previous classifications in the field of surgical pathology of endometrium obtained by the usual methods, namely by biopsy and curettage. In fact, this classification is now used at The Mayo Clinic in the diagnosis of normal and abnormal endometrial tissues.

Subsequent to the studies to which reference has just been made, the characteristics of endometrium associated with malignancy of the body of the uterus have been investigated in 50 cases. For this study sections were made of endometrium from different parts of uterine fundi removed for carcinoma; some of these sections were taken in an endeavor to show endometrium in transition from the nonmalignant to the malignant portion. In addition to this, the ovaries were carefully sectioned in all cases in which the endometrium was studied. Carcinoma of the uterine cervix was entirely excluded from the study since the cervix is, of course, little if any affected by the activity of the ovary except under certain physiologic conditions.

The clinical data were, of course, collected in each case but are not pertinent to the present investigation except with relation to the age of onset of the menopause.

The most confusing factor in studies of this nature to date has been the various attempts on the part of many observers to associate so-called endometrial hyperplasia with the existence or development of carcinoma of the uterus. Such attempts are more confusing than clarifying. One has only to review the reports on this type of hyperplasia to learn that it has been blamed for amenorrhea, menorrhagia, sterility, fibromyoma, abortion, and now, carcinoma. In fact, there is hardly a gynecologic syndrome which has not been associated in some way with this "waste-basket" diagnosis of endometrial hyperplastic change. The studies reported herein present, however, I believe, ample evidence that such a diagnosis is not justified without qualification.

The possible rôle of hyperplasia in association with carcinoma of the endometrium has been suggested by Meyer,[4, 5] Schröder,[6] and Taylor,[7] and, recently, by Novak and Yui.[8] The report of the last named authors is based on the finding of endometrial hyperplasia in 25 per cent of cases of carcinoma of the uterus. Concerning the remaining 75 per cent, no special type of endometrium is described other than atrophic endometrium. Excellent work by Payne[9] has thrown much doubt on the possible causal relationship of hyperplasia to malignancy. He found the incidence of hyperplasia with superimposed or associated carcinoma to be only 2.4 per cent which would indicate a rather rare relationship if such ever occurred. Likewise, Burch stated, "I have never seen the two conditions associated together in the same patient, nor have I ever seen hyperplasia as a forerunner of cancer." With this statement I thoroughly agree. The mere fact that the statements are so widely divergent is ample evidence that "hyperplasia" is a most useless and confusing term and represents a microscopic diagnosis which is of little value. Certainly, the process can hardly be related to malignancy in the light of the reports available to date.

In study of microscopic sections of endometrium taken from portions not involved in malignancy, and of sections taken from portions adjoining the malignant tissue, I have been able to classify the endometrium in terms corresponding to those used to describe the tissue characteristic of the various phases of the cycle; these terms are explained earlier in this report. Casual examination of the illustrations will at once indicate that in practically every specimen the endometrium was similar to that seen in the early or late proliferative phases of the cycle. This type of endometrium always results from the action of estrin (follicular hormone) on the endometrium.

Fig. 6 represents the endometrium of a patient, aged 52 years, who had an adenocarcinoma, Grade 1, of the endometrium. The endometrium is nearly identical with that of a menopausal patient (Fig. 7). The glands are of the small, straight, tubular type and are lined with low cuboidal epithelium of the proliferative type. The ovaries of this patient contained many cysts, lined by granulosa cells, and histologically identical with the ordinary follicular cysts. There were no corpora lutea. The gross thickness of this endometrium was approximately 0.5 mm. and obviously was not hyperplastic.

Fig. 8 likewise represents a specimen of endometrium removed from a patient 61 years of age, who had not menstruated for six years until one month before operation for carcinoma of the uterus. This endometrium was not atrophic nor was it

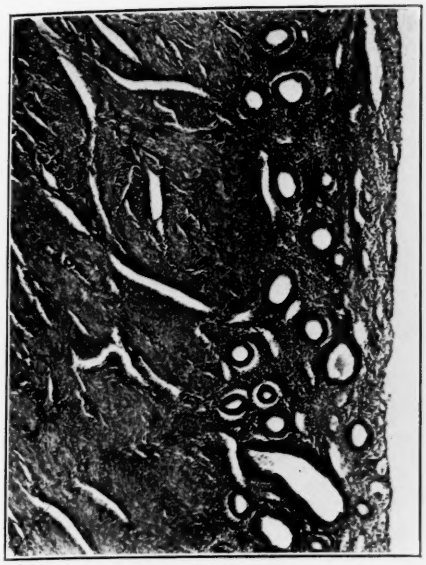

Fig. 6.

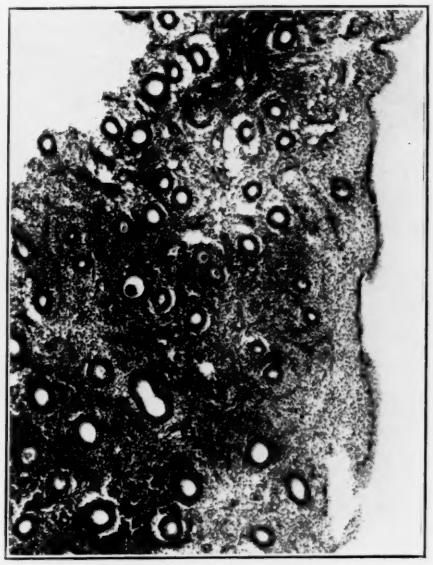

Fig. 7.

Fig. 6.—Persistent early proliferative type of endometrium. Photomicrograph of a specimen removed near an area of malignancy of the fundus. Hematoxylin and eosin (×50).

Fig. 7.—Typical persistent early proliferative phase. Specimen removed from a patient who did not have malignancy but who was in her menopause. Histologically almost identical with Fig. 6. Hematoxylin and eosin (×50).

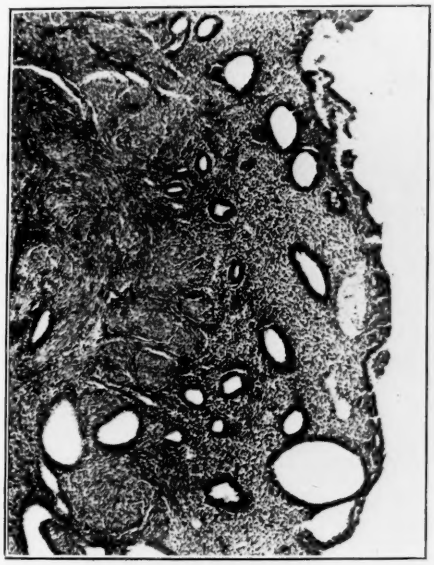

Fig. 8.

Fig. 9.

Fig. 8.—Proliferative type of endometrium with cystic change. Photomicrograph of a specimen of endometrium removed from the fundus of a uterus in which there was a carcinoma. This is a typical early proliferative type of endometrium with cystic change. Hematoxylin and eosin (×50).

Fig. 9.—Early proliferative type of endometrium with cystic change associated with carcinoma of the endometrium. Photomicrograph of a specimen from the same patient as represented in Fig. 8 except that this specimen was removed adjoining the area of malignancy. Note transition from early proliferative type with cyst on the left to an area of malignancy shown on the right. Hematoxylin and eosin (×50).

hyperplastic. It was of typical early proliferative type and cystic change had taken place; this denotes absence of corpus luteum yet a positive effect of estrin. The right ovary in this case contained an adenocarcinoma, Grade 2. The left ovary contained a cyst, 2 cm. in diameter, and several other microscopic cysts. Fig. 9 represents the same endometrium adjacent to the region of malignancy and is of the same type; namely, proliferative in a cystic endometrium.

Fig. 10 represents the endometrium of a patient aged 56 years, who one year after cessation of her menses began to have menorrhagia, which was found to be owing to a carcinoma of the fundus, Grade 1. This specimen of endometrium was removed from a portion in which there was no cancer. This was a typical proliferative type of endometrium with cystic portions which histologically were identical with those previously shown to occur in association with the ovarian failure that is attributable to lack of any luteinizing effect. However, there was definite evidence

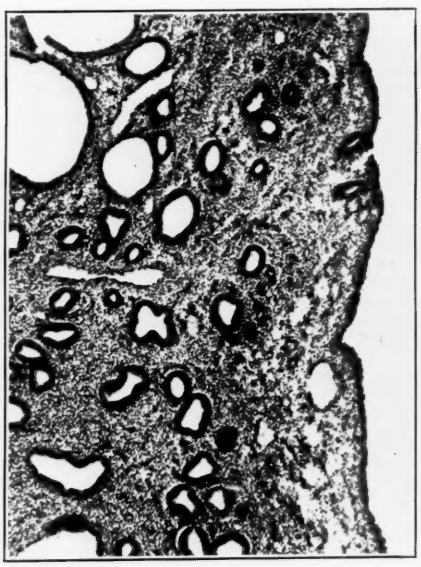

Fig. 10.

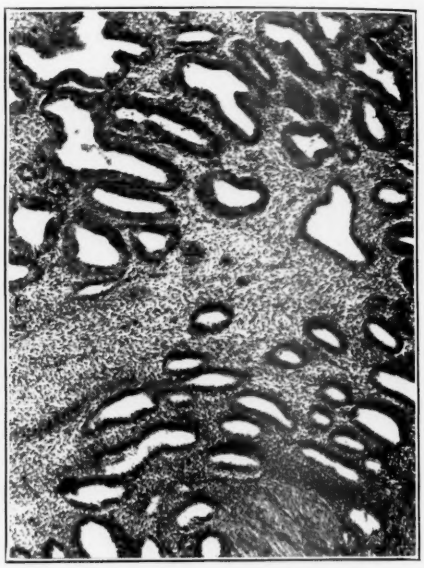

Fig. 11.

Fig. 10.—Proliferative type of endometrium with cystic change. Specimen removed from the endometrium not adjoining the malignant area. This is a characteristic picture of theelin effect and an absence of corpus luteum. Hematoxylin and eosin (×50).

Fig. 11.—Proliferative type of endometrium directly adjoining Grade 1 adenocarcinoma. The left side of this photomicrograph shows a typical adenocarcinoma, Grade 1, while the right side shows a typical proliferative type of endometrium. Hematoxylin and eosin (×50).

of persistent follicular, or theelin, activity and this endometrium was denoted as of persistent proliferative type, with cystic change. Fig. 11 represents the endometrium adjacent to a malignant portion. In the upper right portion of the figure there are normal, or nonmalignant, glands of proliferative type adjoining the area of adenocarcinoma, Grade 1, shown on the left. The ovaries of this patient contained multiple cystic portions, many of which histologically resembled the follicular cyst.

Fig. 12 illustrates the endometrium adjoining the area of adenocarcinoma, Grade 2, of the uterine fundus, removed from a patient aged 54 years, who had experienced the menopause four years before onset of the symptoms which were proved to be attributable to the carcinoma. Microscopically, this illustration shows, on the left, a rather typical adenocarcinoma, Grade 2, and immediately adjoining it an endometrium which is of the persistent early proliferative type and which has undergone cystic change. Both ovaries of this patient contained multiple cystic portions,

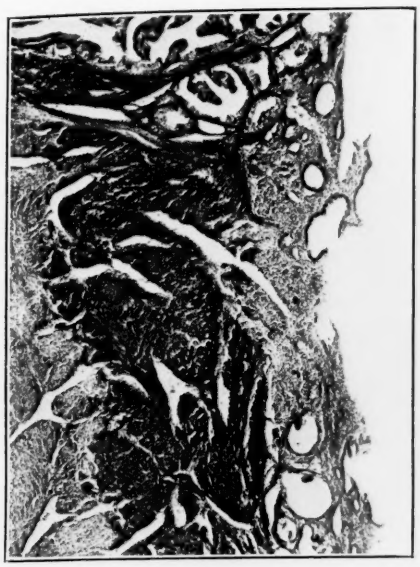

Fig. 12.

Fig. 13.

Fig. 12.—Proliferative type of endometrium with cystic change immediately adjoining an area of adenocarcinoma, Grade 2, of the endometrium. The left portion of this photomicrograph represents a typical carcinoma immediately adjoining the type of endometrium described as proliferative. Note absence of any lutein effect. Hematoxylin and eosin (×50.)

Fig. 13.—The ovary associated with malignancy of the fundus. This is a photomicrograph of a specimen of one of the ovaries in the same case which is shown in Fig. 12. Note the multiple cystic areas, some of which are filled with homogenous material. Hematoxylin and eosin (×50).

Fig. 14.

Fig. 15.

Fig. 14.—One of the cysts shown in Fig. 13 viewed under high power objective. Note the typical granulosa cell lining of the cysts shown here. Hematoxylin and eosin (×200).

Fig. 15.—Early proliferative type of endometrium associated with malignancy. Note the typical early proliferative type of endometrium in the left portion of this figure and the immediate transition to malignancy. Hematoxylin and eosin (×50).

some of which are represented in Fig. 13. One of these cystic portions, photographed at a higher magnification, is represented in Fig. 14. This cyst contains homogeneous material. The wall of the cyst was lined by typical granulosa cells. No corpora lutea were demonstrable.

Fig. 16.

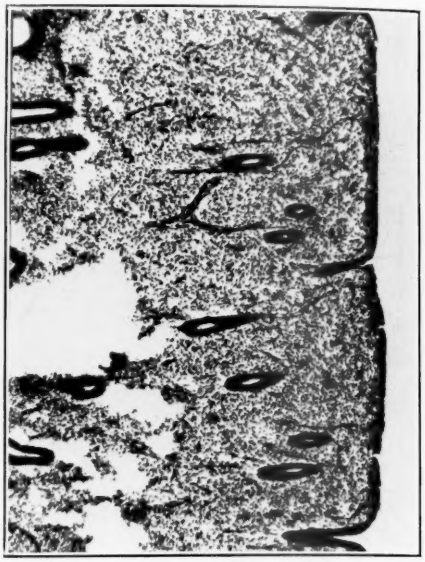

Fig. 17.

Fig. 16.—Early proliferative type of endometrium in transition to malignant area. The lower portion of this figure is a benign, typical proliferative type of endometrium and immediately above it is shown an area of adenocarcinoma, Grade 2. There is no evidence of hyperplasia in any of the figures shown. Hematoxylin and eosin (×50).

Fig. 17.—Early proliferative type of endometrium in association with malignancy. The patient from whom this specimen was removed had not reached her menopause but had a malignant growth in the endometrium. This specimen is almost identical with that shown in Fig. 1, namely, early proliferative type of endometrium due to the action of estrin. Hematoxylin and eosin (×50).

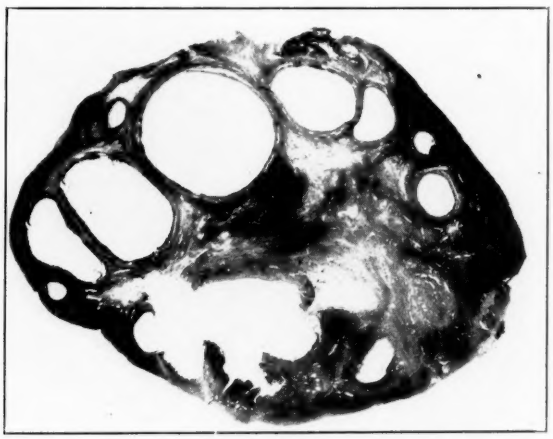

Fig. 18.—Cross-section of one of the ovaries associated with carcinoma of the fundus. Note the multiple cysts, some of which are typical of follicular cysts. Note also the complete absence of any corpus luteum. Hematoxylin and eosin (×3).

Fig. 15, likewise, is of a specimen removed from a patient aged 53 years whose menopause was completed approximately one year before the onset of spotting and bleeding which was proved to be owing to adenocarcinoma, Grade 2. This also was a typical early proliferative type of endometrium, containing one small cyst adjoining a definite area of malignancy. One of the ovaries in this case contained a single cyst.

Fig. 16 represents another specimen which shows a definitely early proliferative type of endometrium immediately adjoining the area of an adenocarcinoma, Grade 2. This specimen was removed from a patient who had had her menopause six years prior to the onset of a pseudocycle, with bleeding and menstrual spotting. This specimen shows no definite cyst but is a typical proliferative type of endometrium. One of the ovaries of this patient contained a carcinoma.

The specimens referred to in the previous paragraphs were removed from patients who had had what could be considered a menopause, followed by the onset of bleeding at intervals after the menopause. Fig. 17 represents the endometrium of an individual aged forty-six years, who was not past her menopause but whose symptoms were essentially those of diffuse menorrhagia, with an interval of three to five weeks for three years, but whose cycle had never ceased. This endometrium, like that of patients past the menopause, was typical of an early or late proliferative type of endometrium and histologically was nearly identical with that represented in Figs. 1 and 2 of this paper, which was obtained from an individual whose endometrium was in the proliferative phase of the normal cycle. The endometrium represented in Fig. 16, therefore, denoted not hyperplasia but merely presence of activity of theelin and absence of any luteinizing or differentiating effect. There were bilateral cystic ovaries also in this case.

Fig. 18 represents the typical, rather characteristic type of ovary found in most of these cases in which the endometrium was the site of malignancy. The endometrium of the noncancer-bearing portion of this patient's uterus was of the typically early proliferative type, with cystic change. In Fig. 18 are represented multiple cysts lined with granulosa cells.

The foregoing are rather typical specimens of the entire series studied, in all of which the type of endometrium was essentially the same. The results of the type of endometria associated with malignancy and the ovarian findings in the 50 cases are shown in Table I. The time between cessation of menses and onset of symptoms suggesting malignancy did not alter the type of endometrium. Of especial interest is the fact that in all except 2 cases the endometrium was of the proliferative type even though 13 (26 per cent) had not reached the menopause, and were still on definite cycle. There was complete absence of differentiation and no corpora lutea were present in the ovaries. In addition to the cystic changes, the ovaries of 10 per cent of these patients contained

TABLE I.—SUMMARY OF STUDY OF ENDOMETRIUM AND OVARIES ASSOCIATED WITH MALIGNANCY OF THE UTERINE FUNDUS; 50 CASES*

TYPE OF ENDOMETRIUM	CASES	PER CENT	OVARIES	CASES	PER CENT
Proliferative without cystic change	14	28	Cystic without malignancy	12	24
			Cystic with malignancy	1	2
			Not cystic	1	2
Proliferative with cystic change	34	68	Cystic without malignancy	23	46
			Cystic with malignancy	7	14
			Not cystic	4	8
Differentiative	2	4	Cystic without malignancy	2	4
			Cystic with malignancy	0	0
			Not cystic	0	0

*In 13 cases (26 per cent) the patients had not reached menopause.

cystic or solid adenocarcinomas which were not metastatic except in one case. This emphasizes the importance of routine bilateral oophorectomy (Table I).

It is difficult to establish the fact that cysts such as occurred in the ovaries of the patients studied are productive of estrin, since there may be sources of estrin other than those known at present. It is true, however, that Fluhmann[10] has been able to demonstrate the presence of estrin in the blood of patients in the postclimacteric period when, as is known, cancer occurs; that is, approximately 75 per cent of cancers of the body of the uterus occur when patients have passed the menopause. An effort has been made in this study to determine the presence of output of estrin by individuals who have cancer of the uterus and the determinations herein reported were made on the urine. Recently I have been able to collect twenty-four-hour specimens of urine in 10 cases in which carcinoma of the uterus was proved to be present, and in 8 of these (80 per cent) positive values for estrin, in amounts of 5 rat units or more, were demonstrable. These patients were in the postclimacteric state and the positive values are, therefore, not owing to the regular menstrual cycle. This observation is particularly interesting in view of the fact that histologically evidence is available in the endometrium, as well as in the ovary, of the presence of this hormone, a fact which is demonstrated by this series of cases.

Analysis of Data on Carcinomatous Endometrium.—Of the 50 cases of endometrial carcinoma of the fundus studied, in 48 (96 per cent) the endometrium was of the proliferative type. In 71 per cent of these 48 cases, the endometrium was of early proliferative type and was associated with cystic change. It has been definitely shown, in the foregoing studies, that this type of endometrium is owing to continued follicular (estrin) activity and failure of the corpus luteum. This type of endometrium is not the so-called hyperplastic endometrium and the diagnosis "hyperplastic endometrium" has led to much confusion in attempts to correlate the endometrium of noncancer-bearing portions with that of cancer-bearing portions. In only 4 per cent (two cases) of this series of 50 cases was a diagnosis of differentiative type of endometrium allowable. The ovaries of both of the patients concerned contained normal corpus luteum; this constitutes still further evidence of the differentiating effect of corpus luteum.

Microscopic and macroscopic cysts of the ovary, lined by granulosa cells typical of follicular cysts, were demonstrable in 90 per cent of the cases in which carcinoma arose in the endometrium. That these cystic portions are possible sources of folliculin is easily possible from a histologic standpoint. Corpora lutea were usually absent. Twenty-six per cent of the patients were in the menstruating age, a fact which would indicate that the absence of corpora lutea in the ovaries was not owing to menopausal or postmenopausal factors but rather it would seem that the absence of corpora lutea is a true accompaniment of the lesion in the endometrium.

It is of interest that castration produces sudden cessation of action of both ovarian hormones on the endometrium and that the histologic result in the endometrium is production of a truly atrophic endometrium. However, gradual ovarian failure, such as occurs in the menopausal state or in association with ovarian dysfunction of younger women, usually is owing to the failure, first, of the corpus luteum; the result, for a time, is a persistent follicular (or estrin) effect. This, in turn, results in the production of an entirely different type of endometrium, namely, a persistent proliferative type, usually with cysts.

The persistent proliferative type of endometrium has been shown by this work to be definitely indicative of the unopposed action of the follicular hormone, and this was the type of endometrium encountered in 96 per cent of the fifty cases studied. It is not a hyperplastic endometrium but rather an endometrium which denotes the presence of the action of theelin. What has been said leads to perhaps one of the most arresting observations made in this work, namely, *that I never saw a carcinoma of the endometrium in the uterus of a previously castrated individual.*

GENERAL SUMMARY

The activity of the ovary is reflected in the activity of the endometrium. The normal endometrial cycle can be divided into the menstruating phase, a phase of early proliferation, a phase of late proliferation, a phase of early differentiation, and a phase of late differentiation. The four last named phases correspond roughly to the four weeks of the normal menstrual cycle in the order named. The abnormal endometrial cycles, which are owing to abnormal ovarian activity, reflect themselves in arrest of the cycle in any of the phases named above. The phase of arrest is called the persistent phase and the stage of arrest depends on the degree and kind of ovarian dysfunction.

The clinical classification of ovarian dysfunction can be divided into a primary and a secondary group. The primary ovarian dysfunctions are owing to failure in the ovary itself. The secondary dysfunctions are owing to changes in the ovary which accompany or follow failure of the thyroid or pituitary functions. In both groups the histologic manifestations are the same because, as stated, the endometrium reflects only the activity of the ovary.

The study of cystic changes in the endometrium associated with different phases of the cycle indicates that one can separate to some degree the cases of sterility from those of bleeding dysfunction. When cystic changes are present in the proliferative phase of the cycle, the tendency is greatest toward bleeding dysfunction and to a lesser degree toward sterility. On the other hand, when cystic changes are associated with the differentiative phases, the tendency is greatest toward sterility, while the tendency toward bleeding dysfunction is almost entirely absent.

From study of the endometrium associated with carcinoma of the body of the uterus, it would seem that carcinoma occurs practically always in the proliferative type of endometrium, in which there is usually cystic change. This endometrium is not a hyperplastic endometrium but is an endometrium the characteristics of which result from unopposed action of estrin (folliculin) and from absence or failure of activity of the corpus luteum. Even when carcinoma of the endometrium occurs in the preclimacteric state, as it does in approximately a fourth of the cases of endometrial carcinoma, the endometrium usually is of the persistent proliferative type and only rarely is there any evidence of differentiation or of activity of the corpus luteum. The ovaries associated with fundal carcinoma contain cystic portions which probably are the source of estrin in 90 per cent of the cases of carcinoma. Further evidence in support of the view that this endometrium, in which carcinoma occurs,

is attributable to the presence of the action of the estrogenic hormone, is indicated by the presence of estrin in the urine of patients whose uterine fundi harbor malignant growths. This type of endometrium is markedly different from the true atrophic endometrium which results from castration. Carcinoma of the body of the uterus never has been seen as far as I have been able to determine, if an individual has been previously castrated.

It seems reasonable to conclude that the unopposed action of estrin, with its resulting effect on the endometrium, which is a persistent proliferative type of endometrium with cystic change, is the basic principle at work in the development of malignancy of the endometrium of those individuals who possess the genetic factor necessary for the development of cancer. These findings, based on ample histologic studies, seem most significant in view of the growing evidence for the carcinogenic possibilities of estrin-like and estrogenic substances.

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THE BIOLOGIC SIGNIFICANCE OF THE FETAL MEMBRANES*

The Joseph Price Oration

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I PLAN here to discuss the biologic significance of the fetal membranes. My choice of subject was decisively influenced by the fact that questions of biology are at present of absorbing interest over the entire world. This is true not only in matters of scientific research, but also in the predominantly practical branches of medicine.

Surgery today is based on biology, its chief endeavor being to maintain natural functions as far as possible.

It is known that the fetal membranes consist of the amnion and the chorionic membrane. The latter has its origin in the cells of the trophoblast of the fertilized ovum. A digestive ferment produced by these cells enables the trophoblast to penetrate into the decidual layers of the uterus. This biologic activity makes the implantation of the fertilized ovum possible. But to assure the implantation of the ovum is not the only purpose of these cells. At a later stage of the ovum's development, blood vessels connect the embryonic area with the chorionic mesoblast through the allantois and the body stalk. Thus the

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circulation of the villi is established, which at a certain period constitutes the only means of nutrition for the embryo. As we know, parts of the villi later degenerate and form the chorion laeve. Another part, coming into contact with the decidua basalis, undergoes further development. United with maternal tissues it becomes the placenta and serves the nutrition of the fetus throughout gestation.

The chorionic membrane is not the only one of biologic importance during pregnancy. The amnion, the other membrane of the fetus, is equally important. This membrane originates from the ectoderm of the embryonic area through the development of the embryonic sac. In its further development, the amniotic sac extends downward and inward, gradually filling out the uterine cavity. The secretion of the amniotic fluid during pregnancy is one of its most important functions. It is now an accepted fact that the amniotic fluid is produced by the activity of the amniotic epithelium and that it is not the result of the function of fetal kidneys nor of transudation from maternal blood. This is capable of experimental proof. In this connection I may mention the vital staining experiments of Goldmann and Evans. These authors injected pyrrole-blue into pregnant animals. In the mother's internal organs the surfaces became blue, while in the fetus only the skin and the intestinal canal were affected. The amniotic fluid was also blue and the amniotic epithelium pigmented, proving that the dye passed into the amniotic fluid through the amniotic epithelium. The fetus became stained only by swallowing the fluid and by being surrounded by it—no trace of the dye was found in the fetal kidneys or urinary tract.

By the secretion of the amniotic fluid the amnion thus accomplishes one of its most important biologic functions, namely, the protection of the fetus. In addition, through the hydrostatic pressure, it protects the placenta, especially during labor, by preventing serious disturbances in the placental circulation, and also hinders the premature separation of the placenta, which otherwise could easily follow the contractions of the womb.

These functions of the membranes are not all they have to accomplish during pregnancy. Beginning at the fourth month, when the fetus, surrounded by the membranes, already fills the entire uterine cavity, they assume a new function by protecting the uterine cavity and consequently the maternal organism, from the danger of ascending infection by vaginal germs. It is unnecessary here to dwell upon the significance of this function, especially important in cases of prolonged labor. We all know for instance the increased dangers connected with a cesarean section made after the rupture of the membranes. We also know that the danger increases with the time elapsed after rupture. The fact that an increased puerperal morbidity and mortality following premature rupture was observed, led to the overestimation of the dangers connected with premature rupture of the membranes. Quite recently it was still universally believed that the membranes play an important part in the dilatation of the cervix.

The observation has frequently been made that in cases of premature rupture of the membranes the period of labor, instead of being prolonged, is manifestly short. In 1934, at the convention of the Hungarian Society of Gynecologists I published my own conclusions, namely that in cases of premature rupture—where no other anomalies such as contracted pelvis, rigid cervix, abnormalities of presentation or mechanism of labor, etc., exist—the delivery takes less time than in cases where rupture occurred normally. In these cases I not only observed the duration of the labor, and especially the duration of the period of dilatation, but I also counted the labor pains. This is a more correct procedure, as far as the judging of the mechanism of labor is concerned, because it tells the number of contractions of the uterus necessary for the complete dilatation of the cervix, and for the expulsion of the fetus. It was found not only that duration of labor was shorter, but also, and this is more convincing, that fewer pains were necessary for the complete dilatation of the cervix than in cases of intact membranes.

Pataky, one of my collaborators, confirmed my earlier observations. I was sincerely gratified to learn that these facts, to which I had called attention in Europe, had also been proved by various American authors.

This question was also taken up by several other European obstetricians: Guthman, Endres, and, later on, Sunde and Wichmann arrived at the same conclusions and confirmed my findings.

Even at the time I first observed this phenomenon, I raised the question of revising the general belief as regards the importance of the membranes in the dilatation of the cervix. The experiences of American authors, such as Gutmacher and Douglas, and Wilson and Slemons, point in this direction. These observers, having the practical consequences in mind, took a step further and, in order to shorten the time of labor, advocated the artificial rupture of the membranes at the beginning of labor.

Following our observations on the results of premature rupture, Dr. Pataky, my assistant, began to follow up the question of early ruptures, or, in other words, cases in which the rupture occurs after labor pains have started but where dilatation of the cervix is not yet complete. I would like to emphasize the reliability of the diagnoses of early ruptures observed in these cases at my clinic. This, because in all those cases the condition of the external os was determined by vaginal examination. I stress this point because at my clinic vaginal examinations are made only exceptionally in cases where labor does not progress and where no information as to the reasons for this can be gained by external or rectal examination. My experiences, gained from the observation of premature and early ruptures of the membranes, obviously tend to prove that the membranes are not of so great an importance for the dilatation of the cervix as was hitherto presumed. Somebody might ask (as was actually done at the above-mentioned Congress in Hungary), For what purpose did nature, then,

provide the membranes? My answer is: They are here to protect the fetus and the circulation of the placenta, and to keep infection away from the mother. That they also have a biologic significance during labor is shown by those cases of prolonged delivery in which the rupture is premature or early and where, later, the cavity of the uterus becomes infected, as indicated by a rising temperature in the patient during labor, or later, in the puerperium. But this danger exists only in cases where other anomalies are also present. My own experience concerning premature ruptures and the observations on early ruptures by Pataky prove that puerperal morbidity and mortality are on the same level as in other cases, provided that the early or premature rupture is not complicated by other, labor-prolonging anomalies. I do not wish to say, that premature and early ruptures may now be regarded as harmless complications. As confirmed also by our own experiences, they are of no special importance in favoring puerperal infections except in those cases where other anomalies impeding a short labor are non-existent. On the contrary, if there exists another cause for prolongation of labor (contracted pelvis, rigid os, anomalies of presentation or of mechanism of labor), premature and early ruptures should be taken very seriously because, during prolonged labor, numerous possibilities for an ascending infection are present. This fact is also revealed in the paper published on the subject by one of my assistants, Dr. Fátyol. He compared cases of premature rupture of the membranes occurring simultaneously with other complications, with cases in which the premature rupture was the only complication. Not only was the percentage of cases with fever higher (22 per cent) in the former group than in the latter (4.2 per cent) but also the frequency of operations (69 per cent, 3.9 per cent), and the maternal (0.5 per cent, 0.3 per cent), and infant mortality (12 per cent, 0.9 per cent). In any given case it is impossible to know how the labor will turn out. Still less is known in advance about the period of latency, i.e., the time between the moment of rupture and the beginning of labor pains. For these reasons, and in spite of my experience that in cases of simple premature or early ruptures (barring complications) the labor will be shorter, I am partial to a certain conservatism and am not sure about the advisability of rupturing the membranes in order to start labor or to hasten it. Should the labor be prolonged in such a case for some unforeseen reason (weak labor pains, rigid os, etc.), there will be no membrane to protect the uterine cavity from infection and the patient is exposed to grave dangers. On the other hand, and this is a consequence of our convictions, we do not hesitate to rupture the membranes artificially in cases where overdue pregnancy threatens to distort the proportions between fetus and maternal organs, and where labor will not start notwithstanding the administration of the customary medicaments. We also resort to artificial rupturing of the membranes in cases of irregular labor pains during the period of dilatation, in which cases, in our opinion, special indications exist for the rupture.

Here van der Hoeven's observation should be mentioned. He found that in cases where a larger portion of the membranes projects into the os, the dilatation is slowed down and the labor becomes prolonged. If there is only a small amount of amniotic liquor contained within the protruding membranes and the latter are adhering to the external os, the increased contractility of the os may, in Schickele's opinion, lead to a spasm of the os and in spite of the satisfactory pains delivery does not proceed. In such cases artificial rupture of the membranes is indicated.

Having arrived at the conclusion that the membranes have no part in the dilatation of the cervix, or at least a much smaller one than was formerly universally accepted (and still believed by many), the question arises, How is then the process of dilatation to be explained? De Snoo gives a very satisfactory explanation of the part played by the membranes in the dilatation. According to him, the tension at a given part of a sphere is proportionate to the internal pressure and the diameter. Inasmuch as the diameter of the membranes in the cervix, especially at the beginning of the dilatation, is quite small, the tension must be insignificant. This explanation also tends to prove that some factors other than the membranes are responsible for the dilatation. That these factors are not found in the presenting part is shown by those cases where, with high presenting part or even in transverse presentations with ruptured membranes, dilatation will occur. According to de Snoo the dilatation of the os is caused by the activity of the cervix. The contraction of the outer muscular fibers of the uterus during the pains is more complete than that of the internal fibers. Following the contractions of the uterus, the cervix is thus gradually turned to a certain degree.

At this juncture, the results of some recent anatomic research by Stieve must be mentioned. According to his findings the cervix becomes transformed into a cavernous body during pregnancy. The membranes protruding into the cervix flatten this cavernous body and thus dilate the os. This theory seems quite acceptable, but only so far as primiparas are concerned; in multiparas we know that the dilatation of the cervix proceeds in an inward and not an outward direction. In these cases the external os is extended before the internal and therefore the reconciliation of this fact with Stieve's theory of dilatation being caused by the pressure of the membranes on the cavernous body becomes very difficult.

Concluding the discussion of the part played by the membranes in the dilatation of the external os, one may admit some biologic influence of the membranes and also take into account Stieve's theory in cases of primiparas. *But it is also undoubtedly true that the part played by the membranes is only of secondary importance. This, not only because the characteristic mechanism of the dilatation of the external os in multiparas cannot be explained by Stieve's theory at all but, still more, because the question of dilatation is a practical one.* The answer can be founded only on a practical basis, i.e., by observation of

the labor. Those who investigated and observed, just as I did, the phenomena of the dilatation period in cases of premature and early rupture without any other complications, all arrived at conclusions in conformity with my views, maintaining that in the dilatation of the external os the membranes play only a subordinate role. Still, it is perhaps advisable, in view of the skeptics' opinion, to emphasize that the significance of an anomaly can be clearly recognized only if no other complication is present. Just for this reason, the studies touching upon the question of premature and early rupture (and based, I may be permitted to say, on the analysis of antiquated statistical data which do not distinguish between cases with and without complications) are not at all suitable for the solution of this problem.

We see now that the biologic significance of the membranes during the labor lies mainly in the protection of the uterine cavity and of the mother against ascending infections. This gains more pronounced importance only in cases where, on account of other anomalies, labor is prolonged. Our recent experiences and observations show mainly that, in cases without any complications other than a premature or early rupture of the membranes, the first stage of labor becomes shorter than expected.

This observation supports the opinion that the membranes are not so important for the dilatation of the external os as was formerly generally believed and as is still maintained by many. But even in these cases the premature rupture of the membranes may prove disadvantageous on account of the part played by the membranes in hindering the ascending infection. This is especially true in those cases of premature rupture where the so-called "period of latency" is prolonged. That is the reason why we do not, for the induction of labor, employ the artificial rupture of the membranes without careful consideration, in spite of the fact that premature rupture (free from other complications) shortens the labor and lessens the number of uterine contractions. Artificial rupture is very particularly weighed in cases of overdue pregnancy with the slightest disproportion between fetus and maternal organs. If in such a case it should be found later, especially after a prolonged period of latency, that a cesarean section is indicated, the danger to the mother is materially increased.

Having discussed briefly the biologic function of the membranes in pregnancy and labor, I would like to take up the second part of my address, dealing with the biologic functions of the membranes in conditions other than pregnancy and labor. I desire to dwell upon how the membranes, as young tissues of great vitality, could be used in plastic surgery.

One year ago I published the description of three artificially formed vaginas, in which I lined the new-formed vaginal tube with membranes of the fetus. The operation is performed in two stages. One may regard the technique of the first stage, which involves separation of the connective tissues between vagina and rectum, and the forma-

tion of a recess corresponding to the vagina, as fully developed. The lining of this recess with epithelium, the second stage of the operation, may be accomplished by various methods, showing that none of the existing techniques is quite satisfactory. Some authors, Mackenrodt, for instance, lined the cavity with pieces of vaginal tissue taken from other patients following a plastic operation. Others, as Gersuny, Abady, Walter Dannreuther, and Marion Douglas, employ pieces of skin taken elsewhere from the patient's own body. Another technique uses preformed tubes to line the artificial vaginas. Baldwin and Mori, and also Schubert, used pieces of small or large intestine. Some of these operations are imperfect (Mackenrodt, Gersuny, Abady), others are dangerous (Baldwin, Mori), and mainly the methods of Wagner-Kirschner and Schubert can be taken into consideration.

Wagner-Kirschner's method is always preferable on account of its safety. It employs skin grafts (Thiersch) from the thighs. Even if performed by an experienced surgeon, Schubert's method on account of its mortality of 4 per cent should be regarded as a serious operation.

As far as the final results are concerned, Schubert's method has been found superior. Here the epithelial lining of the tube carries a muscular layer, and thus closely imitates natural conditions. The tendency of these tubes to shrink is less pronounced than in tubes prepared according to Wagner-Kirschner's method. I do not intend to discuss the technical details of this operation and wish only to mention some technical drawbacks in connection with Schubert's procedure: Should the intestine, pulled in the anus, slide back, incontinence may result. Fistulas developing between the rectum and the new-formed vagina have been described, as have also abscesses. The rupture of one such abscess may cause a fatal peritonitis. To describe step by step the procedure in lining the artificial vaginal tube with membranes of the fetus would take me beyond the scope of this address. Therefore, I shall limit myself to a summary of my own experiences with this method and, incidentally, bring to your attention one hitherto unknown function of the membranes.

I had the opportunity to examine, nine months after operation, one of the artificial vaginas constructed by me. The inspection disclosed a tube perfectly suited for sexual function. The vaginal secretion was found to contain epithelial cells, leucocytes and Döderlein bacilli. The epithelial cells were decidedly similar to those found in the normal vagina. A bit of tissue was excised from the innermost part of the tube, which shows (Fig. 1) a surface layer of stratified epithelium without a horny layer, just as in the normal vagina. By staining according to Best's method, we found (Fig. 2) that the walls of the artificial vagina also contained glycogen.

The striking appearance of stratified epithelium, replacing the epithelium of the membranes nine months after operation, may be explained in two different ways: Either the stratified epithelium crept in from the introitus into the vagina, or else the epithelium of the

transplant was actually transformed. One may presume that the first explanation fits the case. I remember one of my patients who was operated upon for atresia vaginae. During the operation a hematometra was found with infected, fetid contents. I left the newly formed vaginal tube without a lining, kept open only by tampons. The tube

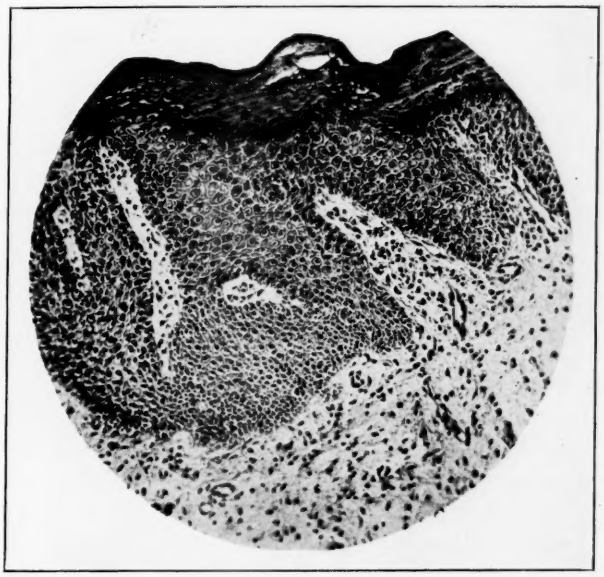

Fig. 1.—The innermost part of the artificial vagina nine months after operation.

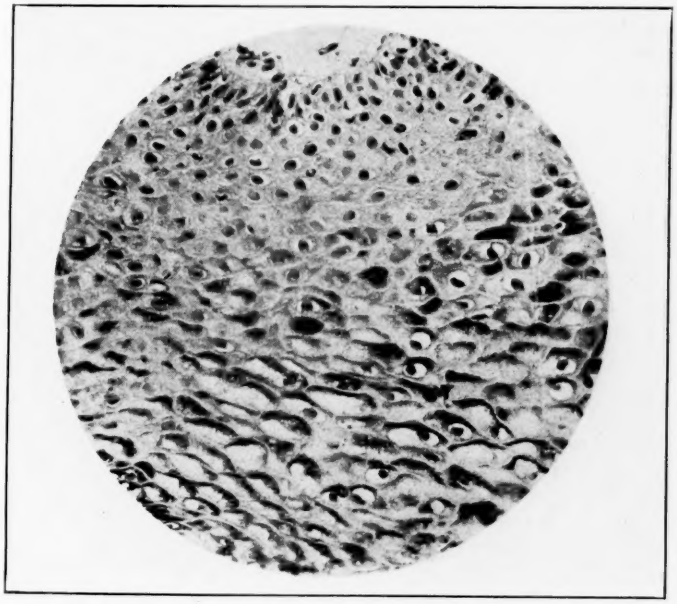

Fig. 2.—The wall of the artificial vagina contains glycogen.

became covered by epithelium in about three months' time. It is improbable that, in those cases where I made a lining from membranes, the epithelization took place in the same manner, because as early as the sixth day we found the membranes adhering perfectly and a smooth tube. The transformation of the epithelium of the membranes appears here to be the most plausible explanation. This is possible because, as we know, the epithelium of the membranes covering the placenta usually consists of two layers, and also because of those familiar little grayish spots in the vicinity of the umbilical cord, the so-called "amniotic caruncles." These show, under physiologic conditions, the same histologic characteristics as the epidermis. It is probable that the amniotic epithelium possesses the faculty of being transformed into the stratified type. That such a transformation may occur in artificially produced vaginas is, to a certain extent, proved by the presence of glycogen, as found by histologic examination. In the amniotic epithelium, glycogen is found under physiologic conditions.

I am aware that there will be contradictions to my statement and doubts as to the transformation of the amniotic epithelium in these cases. Nevertheless, I believe it most probable that the epithelium of the adhering membranes undergoes a transformation in those cases where the operation is performed with adequate precautions to insure sterility, i.e., where the membranes used for lining the tubes are taken from a cesarean section case before rupture of the membranes. My experiences compel me to stress this point. It is quite obvious that the results of such an operation cannot be satisfactory if the membranes delivered through the vagina are used, and still less satisfactory if they are taken some time after rupture and not used immediately after being delivered. The newly formed recess may be regarded as aseptic; an error can be committed only if the membranes used for the lining are not sterile. Obviously, the tube will not remain sterile later on, but then the membranes are already adhering; the important thing is to start the whole process of adhesion under sterile conditions.

To elucidate the question of origin of the stratified epithelium found in the artificial vagina, we performed some animal experiments:

In the first series of these, one eye of a rabbit was enucleated or the conjunctival fold excised. The cavity thus created (or the loss of tissue) was covered with membranes of rabbit fetus, secured by cesarean section. In some cases the membranes adhered to the wound, but these experiments were still not productive of decisive results. It is technically very difficult to work with the extremely thin membranes of the rabbit. In most cases the field of operation became infected. Infection was not the only factor, though very difficult to guard against, which prevented adhesion of the membranes in these experiments. Satisfactory adhesion could not take place under the best of conditions, because these membranes include only a very small amount of chorion.

In another series of experiments pieces of dogs' peritonea were removed and replaced by membranes taken from dogs. Two weeks after the operations there were so many adhesions that we had to count these experiments likewise as unsatisfactory.

The results of the next series were better. A recess was made on the neck of dogs, and this was lined with dog membranes. A section (Fig. 3) shows the opening still present fourteen days after the operation. The microscopic picture (Fig. 4) shows a layer of loose connective tissue moderately infiltrated by leucocytes, separated to a certain extent from a deeper layer of rough connective tissue. The cells of the loose tissue are cuboid, embedded in a network of collagen fibers, and remind one of the connective tissue of the amnion. Some endothelial cells can be seen on the surface.

Fig. 3.

Fig. 4.

Fig. 3.—The recess lined with membranes fourteen days after operation.

Fig. 4.—Loose connective tissue, moderately infiltrated by leucocytes, separated to a certain extent from a deeper layer of rough connective tissue, some endothelial cells on the surface.

Further experiments were carried out on cats: An excised piece of peritoneum was replaced by cat membranes. The conditions found twenty-two days after the operation are shown in Fig. 5. The limits of the transplant are clearly seen, and within these limits are two small, bean-sized, cystlike bodies. Much to our disappointment, the histologic examination revealed the absence of endothelium. The cystlike forms were found to be parts of the transplanted membranes, demonstrating how the latter to a certain extent adhered and lived on.

We also tried to transplant membranes to replace the dura mater in cats. In one of the cases the adherence was satisfactory; still this lone case was not sufficient for the solution of our problem.

After all these unfruitful experiments we concluded that the question could not be answered by animal experimentation.

I approached two of my colleagues, Horvath and Rötth, specialists in diseases of the eye, with the suggestion that they use membrane transplants from the fetus to replace lost conjunctiva in cases of symblepharon. In these cases we also used membranes obtained at cesarean sections, transplanting them as soon as possible after the sections. The results up to the present are very promising. I would like to refer to two of our 6 cases. In a ten-year-old boy, blinded by chalk dust, a symblepharon with corneal scars developed on each eye. The lower lid covered by membrane was free on the tenth day after the operation. A similar case in a woman with contracted symblepharon did not permit the use of an artificial eye. This was successfully operated upon by the same method and the patient now wears an artificial eye.

Fig. 5.—The limits of the transplant on cat's peritoneum, showing two small bean-sized cystlike bodies.

What could not be proved by animal experiments was, thus, demonstrated by operations on the human eye. The fact that in these operations the membranes adhered perfectly, strongly supports, in my opinion, the theory that the epithelium of the transplanted membranes possesses the faculty of being transformed into stratified epithelium. To a certain extent, this would serve as a basis for the experimental production of tissues, so much discussed at present.

Another circumstance supports the view that in cases of artificially formed vaginas the epithelium did not creep in from the outside but was in all probability transformed: A histologic preparation from a case operated upon by Schubert's method is in my possession. This operation was performed in another hospital a year ago. The patient was brought to the surgical department of Dr. Klimko with symptoms of very advanced peritonitis, which proved fatal. Autopsy showed the peritonitis to have been due to rupture of pelvic abscesses. The artificial vagina was taken out and examined: About one-third (the outer third) was covered by epithelium that had crept in from the vulva (Fig. 6). The middle portion of the vagina

possessed no epithelium, and the innermost portion was lined by intestinal epithelium, *not transformed* (Fig. 7).

If the stratified, noncornified epithelium of the walls of the artificial vagina, constructed with the use of membranes, originated from the epithelium creeping in from the outside, then the same thing should have happened here. But nothing of the sort can be found in the intestinal transplant.

That the biologic significance of the membranes lies not only in the possibility of their use in plastic surgery, but that the epithelium of the membranes may also be transformed, is indicated by numerous circumstances. Further experimentation is necessary to enable us to decide whether our cases may really serve as a clinical basis for Spemann's work on tissue induction.

Fig. 6.

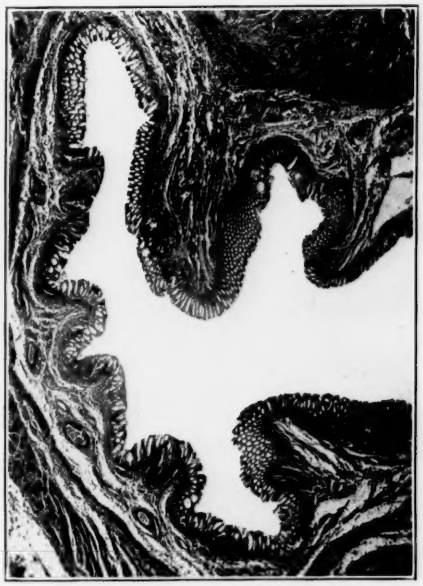

Fig. 7.

Fig. 6.—The outer third of the artificial vagina (Schubert) covered by epithelium, the middle portion without epithelium, and the innermost portion untransformed intestinal epithelium.

Fig. 7.—Untransformed intestinal epithelium on the innermost portion of a Schubert artificial vagina.

We have seen how many-sided is the biologic significance of the membranes of the fetus. But in the light of recent observations and new experiences, this significance is not that still generally believed. The membranes by means of the amniotic fluid produced by them, protect the fetus during pregnancy and also shield the mother from ascending infections from the time the egg fills the entire uterine cavity. They likewise prevent premature separation of the placenta. The part played by them in the dilatation of the cervix during labor is not as important as we have believed, and taught up to the present.

Instead of this we are becoming acquainted with perhaps promising possibilities for the use of membranes in the most ideal field of surgical work, plastic surgery.

The results of operations forming artificial vaginas and the success of certain eye operations seem to point in this direction. There is hope that the young tissues of the membranes, endowed as they are with great vitality, can be similarly used in other cases, e.g., for the covering of burns.

BEHAVIOR OF THE BASAL METABOLISM IN THE COURSE OF DEVELOPING TOXEMIA OF PREGNANCY: CORRELATION WITH CHOLESTEROL, PLACENTAL INFARCTS AND RETINAL EXAMINATION*

A Study of 62 Consecutive Adolescent Colored Primigravidas

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IN THE Prenatal Clinic and Lying-in Ward of the Colored Division of Grady Memorial Hospital, we have long been aware of the fact that an unusually high percentage of the cases of toxemia of pregnancy occurs among adolescent primigravidas not over 18 years of age. Upshaw,[1] Colvin,[2] Acosta-Sisson and Baens[3] and numerous other observers have likewise noted the high incidence of toxemia among primigravidas, nevertheless, as Titus[4] has stated, no satisfactory reason has been advanced to explain the predisposing factor of primiparity.

Bearing this fact in mind, it seemed to us that the hidden factors in toxemia are more concerned with the age of the patient than with the question of parity and that if the primigravida is more prone to develop toxemia it is due to the fact that she is usually young rather than the fact that she is carrying her first child. Close observation, therefore, of a group of adolescent primigravidas should afford a better opportunity to discover facts which would throw some light on the etiologic factors concerned in this disease of many theories.

In our previous studies[5-8] we found evidence to support the theory that toxemia of pregnancy is probably due to toxic products of autolysis of acute placental infarcts, which, in turn, are the result of a specific type of vascular disease of the placental arteries brought about by the combined factors of hypercholesteremia of pregnancy and the trauma of fetal movements on the exposed placental vessels.

Since it has long been recognized that hypothyroidism is associated with hypercholesteremia and hyperthyroidism with hypocholesteremia, it would seem that if adolescent primigravidas showed a tendency to

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hypothyroidism and an exaggerated hypercholesteremia, the latter finding might explain the higher frequency of toxemia of pregnancy in this age-group, through a greater liability to cholesterol-induced vascular change in the placental arteries. Other investigators[11-13] have already noted a greater incidence of toxemia of pregnancy in patients showing hypothyroidism early in pregnancy, but have offered no explanation of the mechanism by which it is produced.

Adolescent primigravidas, registering from time to time in the prenatal clinic during the first trimester of pregnancy, were referred to a special clinic personally supervised by one of us (E. D. C.). In addition to the routine prenatal observations, an initial retinal examination, basal metabolism determination and whole blood cholesterol estimation were made. At intervals of two to three weeks these additional examinations were repeated, and more frequently if any evidence of toxemia appeared.

In this manner it was possible to study the behavior of the basal metabolism, changes in the blood cholesterol and changes in the retinae before, during, and following the development of toxemia, and correlate each with the others and with the clinical evidence of toxemia.

At the time of delivery a specimen of cord blood was saved for cholesterol estimation, and the placenta was prepared and fixed in 10 per cent formalin solution. After fixation for several weeks or more, the placentas were studied as "unknowns" by one of us (R. A. B.)[8] to further verify the fact that the placentas from cases of toxemia show infarcts of the more acute type, whereas placentas from normal cases do not show these lesions.

We are indebted to the Department of Ophthalmology and particularly to Dr. A. V. Hallum for practical instruction given the authors over a period of two years preceding this study, during which time we were acquainted with the ophthalmoscopic diagnosis of the simpler fundamental retinal changes such as edema, changes in the arteriovenous caliber ratio, recognition of angiospasms, arteriovenous compression, increase in arterial light reflex, periarteritis, retinal detachment, and the presence of hemorrhages and exudates. In patients in whom toxemia of pregnancy developed, we availed ourselves freely of consultation regarding the interpretation of questionable lesions and have come to appreciate the immense practical value and importance of retinal examination in the diagnosis and prognosis of toxemia of pregnancy.

Patients who developed clinical evidences of toxemia, were admitted to the hospital for observation. Labor was induced if there was no response to the usual treatment. In spite of these measures three patients developed eclampsia before labor was induced. Six weeks after delivery, a final examination was made, at which time blood pressure, urine, ophthalmoscopic, whole blood cholesterol and basal metabolism examinations were made for comparison with the antepartum findings.

Before discussing the results of the above-mentioned examinations, it should be emphasized at once that the incidence of toxemia of pregnancy in this series of 62 adolescent colored primigravidas was unbelievably high. Twenty-four patients, or 38.7 per cent, became toxic, 9, or

14.5 per cent, showing mild to moderate toxemia, 11, or 17.8 per cent, showing pre-eclampsia, 3, or 4.9 per cent, developing eclampsia, and 1, or 1.5 per cent, developing abruptio placentae.

For the purpose of comparison, 100 consecutive primigravidas from 25 to 30 years of age, from the authors' private cases, were studied, inasmuch as it was found that almost all colored patients in this age period had already become parous. Twenty-one (21 per cent) were found to have developed toxemia, 12 (12 per cent) showing mild to moderate toxemia, and 9 (9 per cent) showing pre-eclampsia. There were no cases of eclampsia or abruptio placentae. It will thus be seen that toxemia occurred nearly twice as often in adolescent primigravidas as in mature primigravidas (Table I).

The results of this study are presented under the subjects of basal metabolism, blood cholesterol, placental infarcts, and retinal changes, following which a correlation of these findings is undertaken, and an effort made to determine wherein these facts support or disprove the theory of the placental origin of toxemia of pregnancy.

TABLE I. INCIDENCE OF TOXEMIA IN ADOLESCENT (13 TO 18 YEARS) AND IN MATURE (25 TO 30 YEARS) PRIMIGRAVIDAS

AGE GROUP	NUMBER OF CASES	MILD TO MODERATE TOXEMIA	PRE-ECLAMPSIA	ECLAMPSIA	ABRUPTIO PLACENTAE	TOTAL NO. TOXIC CASES
13 to 18	62	9 (14.9)	11 (17.8)	3 (4.9)	1 (1.5)	24 (38.7)
25 to 30	100	12 (12.0)	9 (9.0)	0 (0.0)	0 (0.0)	21 (21.0)

BASAL METABOLISM

Talbot and others[9] state that in the female, the basal metabolism increases from the age of 10 to the onset of menstruation. It then falls until, between the fifteenth and sixteenth years, it is 5 per cent below the average trend. They further state that available data indicate that climate and geographic location influence metabolism more than race, as shown in Table II.

We believe, as Litzenberg[10] has already stated, that "deviations from the normal rate must be due to thyroid influence," since the vast majority of patients with hypometabolism responds to thyroid therapy. While the literature on the subject of basal metabolism in pregnancy has become quite voluminous, very little has been published bearing on the subject matter herein presented.

TABLE II. COMPARISON OF BASAL METABOLISM RATES RECORDED BY DIFFERENT OBSERVERS THROUGHOUT THE UNITED STATES*

OBSERVER	LOCATION	AGE	NUMBER OF CASES	DEVIATION PER CENT (WEIGHT)
Talbot	Boston	10-19	87	0
Lucas	San Francisco	8-18	207	− 1
Stark	Wisconsin	9-16	52	− 2
Topper	New York	10-16	39	+ 4
Blunt	Chicago	8-17	58	+ 3
McKay	Ohio	13-18	80	− 7
McKittrick	Wyoming	17-26	100	− 9.9
Stark	Wisconsin	17-20	86	−12
Remington & Culp	South Carolina	18-20	37	−10
Coons	Oklahoma	17-22	99	−16
Hilt	Florida	17-20	40	−14

*Figures are from Talbot, Wilson and Worcester.

Bloss[11] has noticed an increased tendency to toxemia among women who have low metabolic rates early in gestation. He also noted that the placentas from women with hyperthyroidism late in pregnancy, showed much degenerative change with hemorrhage and infarction. Taylor[12] has likewise noted a tendency to eclampsia among women with low metabolism early in pregnancy.

Hughes[13] in studying 1250 basal metabolic determinations in pregnancy, noted a decrease in rate during the second, third, and fourth months, followed by a gradual increase, reaching a maximum in the third trimester. Plass,[14] Baer[15] and others also noted the maximum elevation occurred toward the end of gestation, followed by an appreciable drop in the puerperium. The tendency to a rise in the basal metabolism late in pregnancy has not, heretofore, been suspected of being a part of the clinical picture of toxemia.

TABLE III. AGE DISTRIBUTION OF 62 ADOLESCENT PRIMIGRAVIDAS

13 years	3 cases
14 years	2 cases
15 years	6 cases
16 years	15 cases
17 years	20 cases
18 years	16 cases

The patients in this series, were instructed to eat a light evening meal and take neither food nor liquid from midnight on until the test was made, between 7:30 and 9:30 A.M., preceded by a short rest period. A light portable bedside apparatus was used.

The ages ranged from 13 to 18 years, inclusive, and were distributed as shown in Table III.

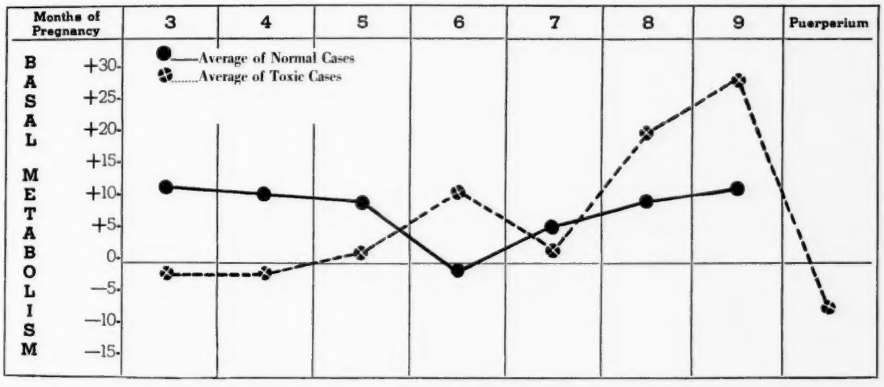

Fig. 1.—Behavior of basal metabolism throughout pregnancy in 38 normal and 24 toxic adolescent primigravidas.

As previously mentioned, 24, or 38.7 per cent, of the patients presented clinical evidence of toxemia of pregnancy. In Fig. 1 the average of the basal metabolic determinations of all toxic and nontoxic cases have been plotted for each calendar month of pregnancy. Unfortunately, for the purpose of comparison we failed to follow the nontoxic patients during the puerperium. However, several observers have previously noted an appreciable drop in the basal metabolic rate in the puerperium.

Analysis of the results showed that the initial basal metabolic rates of the 38 normal cases (solid line and dots) presented variations ranging from plus 2 per cent to plus 18 per cent. The average reading throughout pregnancy, was between plus 5 and plus 16 per cent, except in the sixth month when it showed a substantial drop. With this exception, the curve closely parallels the results obtained by previous investigators.

In the group of 24 toxic cases the initial basal metabolic readings in the third month varied between plus 9 and minus 22, the majority of the readings being between minus 5 and minus 12 per cent. It will be noted that the average basal metabolic rate was less than zero during the third and fourth months, but the individual rates fluctuated over a much wider range than did the normal after the fifth month.

However, without exception, at the onset of clinical symptoms and signs of toxemia of pregnancy, the basal metabolic rate sharply increased to levels far above those previously noted in the earlier months of gestation. The increase in rate varied in individual cases between plus 20 and plus 55 per cent. In some cases an unexplained rise occurred even before well-marked evidences of toxemia were present, making it possible to predict the probable development of toxemia at an early date. Cases which showed a trend in rate from minus 10 in the third month to plus 10 in the seventh month and then suddenly increased to levels of plus 35 to plus 55 per cent, were always associated with severe toxemia, pre-eclampsia, eclampsia, or abruptio placentae. The less pronounced rises to levels of plus 25 to 30 per cent in the eighth or ninth months were usually associated with a less severe degree of toxemia.

It is our impression that the sudden elevation in basal metabolism, accompanying the onset and continuing throughout the course of toxemia of pregnancy, is the result of sudden increase in thyroid activity, brought about by excessive stimulation of the gland by the poisonous autolytic products of acutely infarcted placental tissue.

To determine whether the initial basal metabolic rate at the third month is of any prognostic significance as to the possible development of toxemia later in pregnancy, the cases were divided into four groups: (1) readings of less than minus 10; (2) readings from minus 10 to zero; (3) readings from zero to plus 10; and (4) readings of plus 10 or above. Table IV shows the number of cases and the incidence of toxemia in each group.

TABLE IV. INCIDENCE OF TOXEMIA IN 62 ADOLESCENT PRIMIGRAVIDAS ACCORDING TO INITIAL BASAL METABOLIC RATE DETERMINATIONS AT THIRD MONTH OF PREGNANCY

BASAL METABOLISM	NUMBER OF CASES	NORMAL	TOXEMIA	PER CENT
−22 to −10	4	2	2	50.0
−10 to 0	26	11	15	57.7
0 to +10	20	13	7	35.0
+10 to +24	12	12	0	0.0

In the group showing initial basal metabolic readings of plus 10 or more, there were no cases of toxemia; from zero to plus 10, 35 per cent developed toxemia; from minus 10 to zero, 57.7 per cent developed toxemia; and below minus 10, 50 per cent developed toxemia. The number of cases in the last group is too small to permit accurate conclusions, but with the evident trend to more frequent toxemia, the lower the metabolic rate, it might well be that a larger number of cases would show a still higher frequency of toxemia in this group.

It appears, therefore, that the basal metabolic rate as determined in the first trimester of pregnancy, bears a direct relation to the incidence of toxemia in the last trimester of pregnancy. It also appears that the liability to toxemia is great even though the basal rate is within the limits commonly accepted as normal—minus 10 to plus 10, but that there is little or no liability to toxemia if the initial rate is found to be more than plus 10. From a therapeutic standpoint, these findings give promise of great possibilities in the prevention of toxemia, if appropriate treatment is instituted early in pregnancy.

At the present time we are making a study of the effect of adequate doses of thyroid extract in those cases showing initial basal metabolic readings below zero, to determine to what degree toxemia of pregnancy can be prevented.

CHOLESTEROL

As previously mentioned, Hurxthal,[16] Luden,[17] Epstein and Lande,[18] and Mason, Hunt and Hurxthal[19] have shown, by clinical or animal experiments, that in hypometabolic states, the blood cholesterol is increased, whereas in hypermetabolism, it is decreased, and that this inverse relationship holds true whether brought about by pathology of the thyroid gland or by administration of desiccated thyroid.

Turner, Present and Bidwell[20] demonstrated an increase of 19 per cent in blood cholesterol in rabbits, following total thyroidectomy, but the increase was much more marked (137 per cent) in rabbits with experimental hypercholesteremia previously induced by cholesterol feeding. Hunt, Patterson and Nicodemus[21] found the average blood cholesterol elevated in each lunar month of pregnancy, but with variations in individual patients, some showing an unexplained drop in the ninth and tenth lunar months. The administration of thyroid extract caused a drop in the blood cholesterol, which rose to its former level when thyroid extract was discontinued. Dieckmann[22] found no significant difference between the average plasma cholesterol values of a series of pre-eclamptic cases and a series of normal pregnancies, but concluded the values were much higher in the former.

The results of the basal metabolic studies in our series of cases indicated that hypothyroidism definitely predisposed to the development of toxemia in pregnancy. Since hypothyroidism is associated with hypercholesteremia, and hypercholesteremia is the necessary antecedent to cholesterol vascular change in the placental arteries, by which rupture, thrombosis or embolism are produced with resulting placental infarction and toxemia, it was necessary to study the blood cholesterol and correlate it with the basal metabolic findings.

The blood collected for cholesterol determinations was obtained between 8 and 9 A.M. at intervals of two to three weeks with the same preliminary preparation as was mentioned regarding the basal metabolism determinations. The modified Blohr technique was employed for estimation of the whole blood cholesterol. The cases were divided into groups according to whether the basal metabolism was (1) below minus 10; (2) minus 10 to zero; (3) zero to plus 10; and (4) plus 10 or above.

The first group was made up of four patients in whom the basal metabolic rate ranged from minus 22 to minus 10. The incidence of toxemia in this group was 50 per cent (Fig. 2).

It will be seen that the normal cases showed an average initial basal metabolic rate of minus 11 which gradually increased to zero in the eighth month, decreasing to minus 2 in the ninth month. The toxic cases showed an average initial basal metabolic rate of minus 12 which gradually increased to minus 4 in the eighth month but with the onset of toxemia in the ninth month, rose sharply to plus 16.

It will also be seen that the average initial cholesterol value was considerably higher in the toxic (236 mg.) than the nontoxic cases (175 mg.) and, except in the sixth month, remained so throughout. Unlike the other groups to be described, however, it did not drop noticeably in the ninth month in association with the rise in the basal metabolic rate and the occurrence of toxemia, neither did it rise post partum with the fall in basal metabolic rate. As mentioned before, the number of cases in this group is too few to draw worth-while conclusions.

The second group is composed of 26 cases in which the initial basal metabolic rate at the third month, ranged from minus 10 to zero. The incidence of toxemia in this group was 57.7 per cent (Fig. 3).

It will be seen that the normal cases showed an average initial basal metabolic rate of minus 3, which, except in the fifth month, remained minus through the seventh and gradually increased in the eighth and ninth months to plus 12. The toxic cases showed a lower average initial basal metabolic rate of minus 6, which remained minus through the fifth month, then rose steadily each month, reaching a maximum of plus 28 in the ninth month. The increase in the ninth month ranged from plus 22 to plus 55 per cent.

It will also be seen that the average cholesterol value in the nontoxic cases showed moderate fluctuations (171 to 207 mg.), but no definite trend or drop during the eighth and ninth months when the basal metabolic rate was showing a moderate increase. The initial average cholesterol value of the toxic cases (219 mg.) was

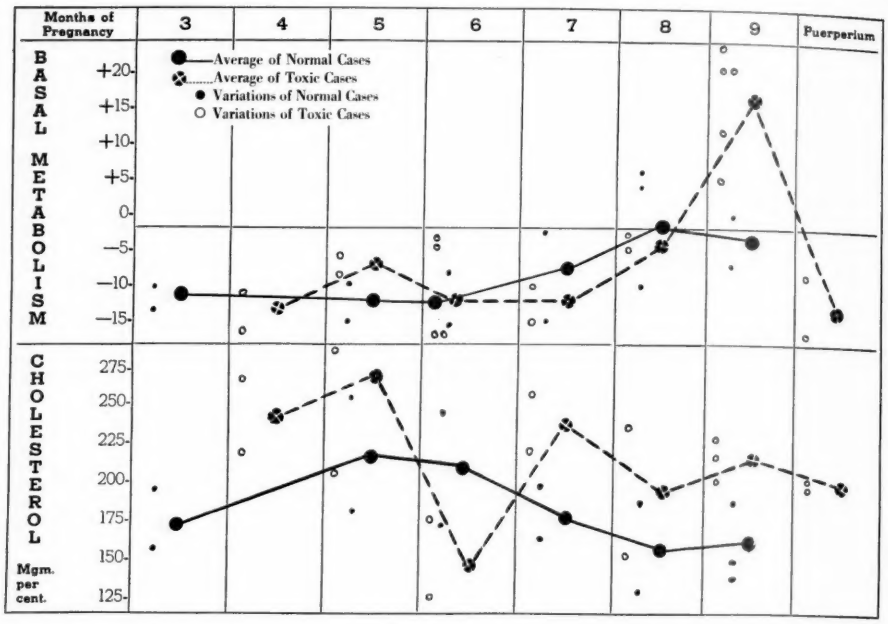

Fig. 2.—Behavior of basal metabolism and whole blood cholesterol throughout pregnancy in 4 primigravidas whose initial basal metabolic rate at the third month was −10 or lower, two of whom became toxic.

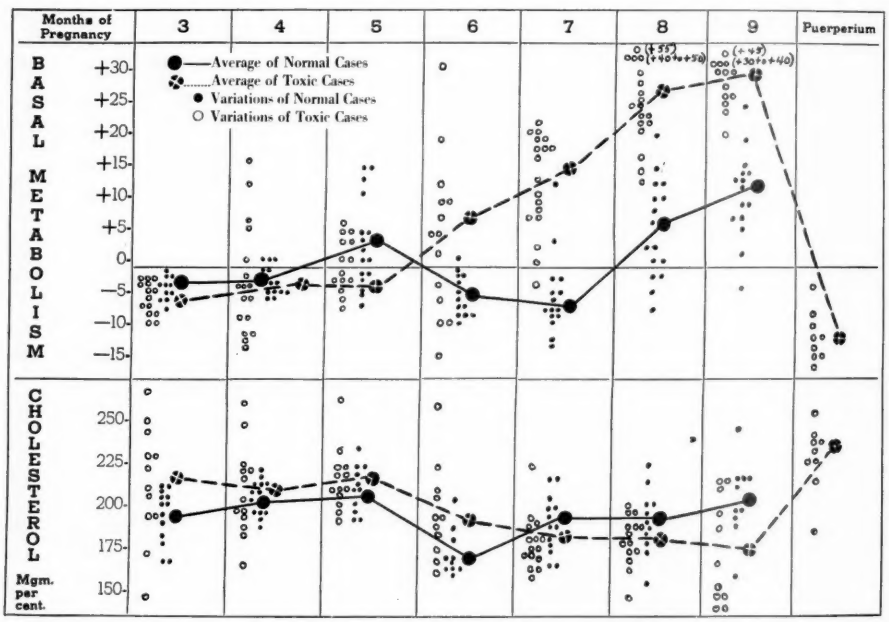

Fig. 3.—Behavior of basal metabolism and whole blood cholesterol throughout pregnancy in 26 primigravidas whose initial basal metabolic rate at the third month was from −10 to 0, 15 of whom became toxic.

considerably higher than that of the nontoxic cases (191 mg.), and showed a definite downward trend to 178 mg. from the sixth month on, during the rise in the basal metabolic rate in association with toxemia. It was necessary to interrupt pregnancy in many of these cases before term.

It will further be seen that with the drop in the average basal metabolic rate of the toxic cases during the puerperium to minus 12, the average cholesterol value rose to 228 mg., even higher than the initial reading.

The reciprocal behavior of the basal metabolic rate and the cholesterol value in the toxic cases, is therefore similar to that which is seen in hyper- and hypothyroid states.

The third group is composed of 20 cases in which the initial basal metabolic rate at the third month ranged from zero to plus 10. The incidence of toxemia in this group was 35 per cent (Fig. 4).

It will be seen that the normal cases showed an average initial basal metabolic rate in the third month of plus 6, which decreased slightly to plus 4 in the seventh

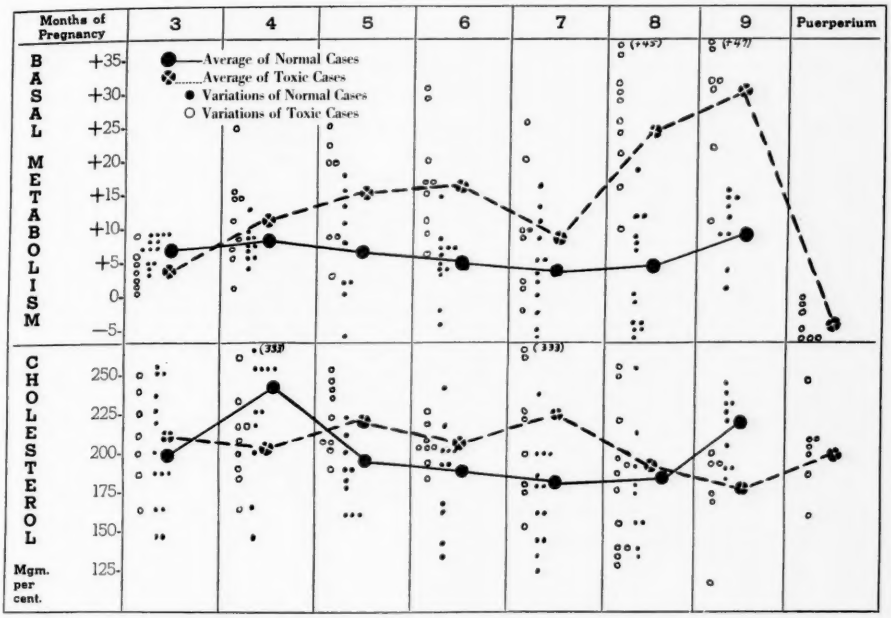

Fig. 4.—Behavior of basal metabolism and whole blood cholesterol throughout pregnancy in 20 primigravidas whose initial basal metabolic rate at the third month was from 0 to +10, 7 of whom became toxic.

month, rising to plus 8 in the ninth month. The toxic cases showed an average initial basal metabolic rate at the third month of plus 4, gradually rising to plus 16 in the sixth month, dropping to plus 8 in the seventh month, then rising sharply to plus 24 in the eighth and plus 31 in the ninth month in association with toxemia.

It will also be seen that the average initial cholesterol value of the nontoxic cases at the third month, of 209 mg. rose to 243 mg. in the fourth month, then gradually dropped to 181 mg. in the seventh month, rising to 193 mg. in the eighth and 218 mg. in the ninth month. The initial cholesterol value of the toxic cases at the third month, of 211 mg. gradually rose in a fluctuating manner to 223 mg. in the seventh month, then dropped sharply to 194 mg. in the eighth and 176 mg. in the ninth month, during the time the basal metabolism was rising sharply in association with toxemia.

It will further be seen that with the drop in the average basal metabolic rate of the toxic cases during the puerperium to minus 4, the average cholesterol value rose 199 mg.

The general trend of the basal metabolism and cholesterol curves in Group 3 (zero to plus 10) is similar to that in Group 2 (minus 10 to zero) and further bears out the similarity in the reciprocal behavior of the basal metabolism and cholesterol to that seen in hyper- and hypothyroid states.

The fourth group is composed of 12 cases, in which the initial basal metabolic rate at the third month was plus 10 or more. None of these patients developed toxemia (Fig. 5).

The initial average basal metabolic rate in the third month, of plus 18, decreased to plus 11 in the sixth and seventh months, rising to plus 22 in the eighth and dropping to plus 15 in the ninth month.

The initial average cholesterol in the third month was 175 mg. and showed no definite trend although there were monthly fluctuations.

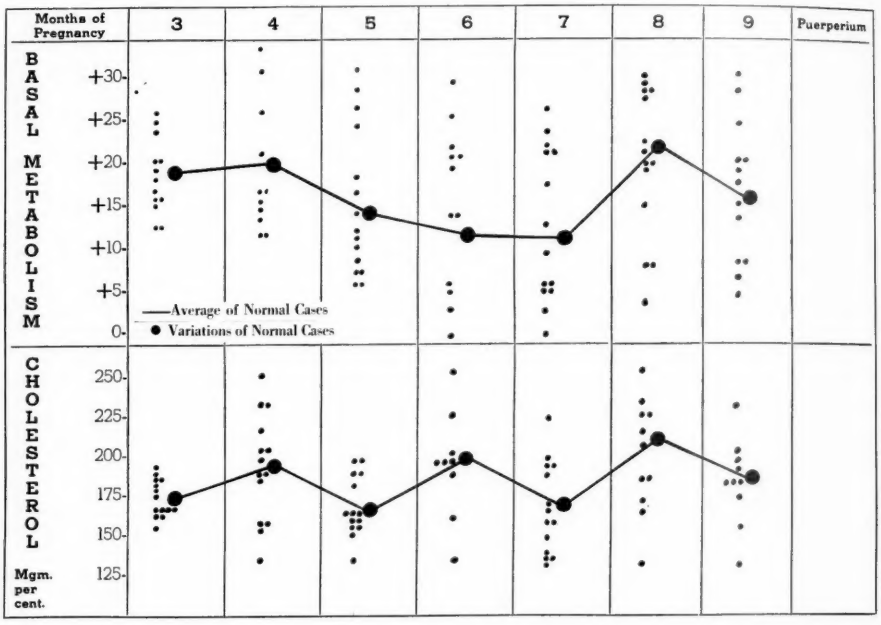

Fig. 5.—Behavior of basal metabolism and whole blood cholesterol throughout pregnancy in 12 primigravida whose initial basal metabolic rate at the third month was +10 or higher, none of whom became toxic.

The average initial whole blood cholesterol at the third month in the four groups is shown in Table V.

In the group showing an initial basal metabolic rate of plus 10 or more (no cases of toxemia), the initial blood cholesterol was 179 mg.; in the group showing zero to plus 10 (35 per cent toxemia) it was 205 mg.; in the group showing minus 10 to zero (57.7 per cent toxemia), it was 204 mg.; and in the group showing readings below minus 10 (50 per cent toxemia), it was 209 mg.

TABLE V. RELATION OF AVERAGE INITIAL WHOLE BLOOD CHOLESTEROL TO BASAL METABOLIC RATE AND INCIDENCE OF TOXEMIA IN 62 ADOLESCENT PRIMIGRAVIDAS

NUMBER OF CASES	WHOLE BLOOD CHOLESTEROL MG. PER CENT	INITIAL BASAL METABOLIC RATE AT THIRD MONTH	INCIDENCE OF TOXEMIA PER CENT
12	179	+10 to +24	0.0
20	205	0 to +10	35.0
26	204	−10 to 0	57.7
4	209	−10 to −22	50.0

While the blood cholesterol values show no significant differences in the groups below plus 10 metabolism, there is a significant drop in the blood cholesterol in the group showing basal metabolic readings above plus 10, in which group toxemia did not occur. This apparently shows that in the presence of hypercholesteremia, the degree of hypercholesteremia is not so important as the factor of trauma of fetal movements on the unprotected arteries on the surface of the placenta, since it has been shown[7] that cholesterol vascular change occurs, not only more rapidly but with less hypercholesteremia if the vessels are subjected to trauma.

The blood cholesterol values in our series are not as high as those presented by Hunt, Patterson and Nicodemus[21] who found an average of 175 mg. at the end of the second month, followed by a gradual increase to 247 mg. at term. Likewise they differ from the statistics of Dieckmann[23] who found in normal pregnancy, an average increase in blood plasma cholesterol of 23 per cent at term. In nonconvulsive toxemia he found values which ranged from 234 to 382 mg. and concluded that there was no significant difference in the level of the blood cholesterol in toxemic and normal pregnant women, but that the values are much higher than in nonpregnant women.

Fetal cord blood was collected at the time of delivery in 58 cases, 35 of which were from normal and 23 from toxic cases. In the normal cases, the cord blood cholesterol ranged from 161 to 189 mg., while in the toxic cases, with only a few exceptions the cholesterol values were lower, ranging from 96 to 133 mg. It would seem reasonable that an increased basal metabolic rate in the mother, in the presence of toxemia, would lower the fetal as well as the maternal blood cholesterol.

It is our belief that the rise in the basal metabolic rate accompanying the development of toxemia is due to excessive stimulation of the thyroid gland from the poisonous autolytic products of acute placental infarcts which result from cholesterol vascular disease in the placental arteries. The increase in basal metabolic rate is in turn accompanied by a drop in the blood cholesterol. This may explain why Slemons and Curtis[24] did not find hypercholesteremia constantly present in eclampsia.

PLACENTAL INFARCTS

The placentas were prepared by removing the membrane, cord and adherent blood, and fixed in 10 per cent solution of formaldehyde for three or more weeks. They were examined by cutting strips 0.5 to 1 cm. in thickness. In order to further test the association of the more acute types of placental infarcts with toxemia of pregnancy, the placentas were studied by one of us (R.A.B.) as "unknowns." It was possible to make a correct diagnosis of the occurrence of toxemia during pregnancy, in 88 per cent of the cases. Except in one case, the errors in diagnosis were due to overlooking very early areas of infarction, rather than diagnosing areas of acute infarction in normal placentas.

In a recent study[8] in which 100 placentas from both normal and toxic cases were examined as "unknowns," it was found possible to classify the infarcts according to the degree of toxemia, and prove the association of a definite placental pathology with toxemia of pregnancy.

Patterson, Hunt and Nicodemus[21] performed complete thyroidectomy on rabbits at the end of the first trimester of pregnancy. Near the end of pregnancy the rabbits developed convulsions and died. Necropsy disclosed toxic nephritis, early toxic hepatitis and pulmonary congestion. The placentas were thicker and darker than normal. On section, beneath the darker surface areas, there were circumscribed black areas, grossly and microscopically characteristic of acute infarcts. The arteries were found to have thickened walls and small lumina and in many vessels the intima was swollen to such a degree by the presence of large fat cells that the lumen was completely occluded.

In the above experiment we do not believe that trauma played a part in initiating cholesterol vascular change in the placental arteries on account of differences in anatomic form and relations in the rabbit's uterus, fetus, and placenta, but of equal, if not more, influence is the fact that the rabbit is an animal peculiarly unable to handle or metabolize cholesterol. Hence, an unusual degree of deposit occurs in the arteries, leading to occlusion and infarction.

In previous experiments[5] we demonstrated that repeated injections of autolysate of placental tissue into guinea pigs produced convulsions and pathologic evidences of toxemia. Injections of autolysates of other tissues caused clinical and pathologic evidences of toxic effects from protein split products, but none of the animals developed convulsions.

The question arises, what is there in the autolysate of placental tissue which causes convulsions to occur in the rabbits or guinea pigs, and why do convulsions fail to occur when the animals are injected with autolysate of other tissue?

We believe the answer to this question is found in the fact that placental tissue differs from all other tissues in its high content of arginine. This amino acid is apparently a necessary component of any tissue which is undergoing rapid growth or has to do with growth. Considering the rapid growth and function of the placenta, one might expect to find that arginine represented a larger percentage of the nitrogen than in other tissues.

Harding and Fort[25] in analyzing placental tissue for its nitrogen components, found that arginine made up 24.08 per cent of the total nitrogen, a strikingly high value which is about twice that of any other tissue. Graff and Graff[26] studying 10 mature placentas found an average arginine nitrogen value of 14.9 per cent. They quote the work of Ehrenberg and Lievenov, who obtained a value of 21.3 per cent. They state that Wehefritz, who found values of 22.8 per cent in a five months' placenta and 13.9 per cent in a nine months' placenta, agreed with Ehrenberg in stating that the arginine content decreases with the age of the placenta.

We believe that the high content of arginine in placental tissue explains the peculiar eclamptogenic power of this tissue through the probable liberation of guanidine from arginine by a series of oxidation reduction reactions during autolysis as described by Parker[6] working with one of us (R. A. B.).

A consideration of the physiologic and pathologic effects of injection of guanidine, cannot fail to impress one with the fact that the symptoms and findings strikingly resemble those found in pre-eclampsia, eclampsia, and abruptio placentae. Titus and others[27] in a summary of the outstanding effects of guanidine intoxication list them as follows: disturbance in carbohydrate metabolism; fluctuation in blood sugar (hypoglycemia); increase in blood uric acid, amino acids, and lactic acid; increase in blood pressure; edema; renal damage and convulsions. To these may be added peripheral vasoconstriction, demonstrated by Major[28] and others.

Several investigators have described the presence of an increased amount of guanidine in the blood of pre-eclamptic and eclamptic women. Minot and Cutler[29] found guanidine concentrations of 0.50 and 0.85 mg. in pre-eclampsia and eclampsia as compared to 0.25 to 0.40 mg. per 100 c.c. of blood in normal pregnancy.

Andes and others[30] found the blood guanidine value in mild toxemia the same as in normal pregnancy, but in severe toxemia there was an additional rise which persisted as long as the toxemia existed. These authors, studying the whole blood guanidine values of 17 normal pregnant women, found an average value of 0.23 mg. In studying the whole blood guanidine values of eight women during the puerperium, they found the average value elevated in every case to almost twice that observed before delivery. This post-partum hyperguanidinemia begins soon after delivery, increasing to a maximum between the third and seventh days, then decreasing gradually to a normal level by the end of the third week.

In our opinion, the probable source of post-partum hyperguanidinemia is autolysis of remnants of villi and the involution of the uterus which progresses so rapidly early in the puerperium.

Although Malmejac[31] arrived at conclusions similar to those of Andes,[30] de Wesselow,[32] and Stander[33] have expressed dissenting opinions concerning the presence of hyperguanidinemia in women with toxemia of pregnancy.

We are not qualified to pass judgment upon the explanations offered for variations in results obtained by different observers, but some of the differences may possibly arise from the fact that the concentration of guanidine in the blood of a toxic patient may vary from time to time according to the amount probably liberated in the blood stream. Experiments have shown that a given amount injected slowly may not be demonstrable in the blood, or produce recognizable effects, but the same amount injected rapidly, produces definite effects and shows increased con-

centration in the blood. If autolysis of acutely infarcted placental tissue is the source of guanidine, as we believe, it is possible that variations in the rate of autolysis may account for lack of uniform results by different observers.

In recent years the discovery that retinal vascular spasm is a frequent finding in association with toxemia of pregnancy, has led to widespread acceptance of the theory that toxemia of pregnancy is a disease of the smaller terminal arterioles and that pathology in the liver and kidney and other organs is secondary to vascular disease. Volhard[34] advanced this theory in 1918. Since then other investigators have expressed themselves in favor of this concept. Irving,[35] Eastman[36] and others conclude that arteriolar spasm is the common factor in toxemia of pregnancy and a clear understanding of the nature of this disease awaits a satisfactory explanation of the cause of arteriolar spasm.

Recent studies have shown that the elevation of blood pressure following injection of guanidine, is due to peripheral vasoconstriction of the smaller arterioles. Barksdale[37] injecting sublethal doses of dimethyl-guanidine sulphate into the peritoneal cavity of the frog and rabbit, noted arteriolar constriction in the frog's foot and the rabbit's ear within four minutes, followed by a return to normal arterial caliber within twenty minutes.

Major[28] sought to determine the mechanism of vasoconstriction following guanidine injection. He ruled out the heart beat as a factor in the associated hypertension, by cutting the vagi, without influence on the blood pressure. As added proof, he registered the contractions of the ventricles and auricles, and noted the carotid blood pressure. The viscosity of the blood was studied, with negative results. Finally, to determine the influence of the central nervous system, the medulla of a dog was removed, followed by injection of guanidine. The blood pressure rose, just as in the nondecerebrated dog. From these studies he concluded that guanidine caused vasoconstriction and hypertension through direct action upon the musculature or the nerve endings in the arteriolar wall.

This work lends support to our belief that the elevation of blood pressure in toxemia of pregnancy, is due to peripheral vasoconstriction of the smaller arterioles, as a result of the action of guanidine directly upon the musculature or nerve endings in the vessel wall.

STUDY OF THE RETINAE

Mylius[38] Wagener[39] Hallum[40] and Mussey[41] have demonstrated that toxemia of pregnancy is associated with spasms and tonic constrictions of the retinal arteries; that the constrictions disappeared if the blood pressure dropped, but became fixed and generalized if it remained elevated and the toxemia persisted; that prolonged severe constriction was followed by localized edema or hemorrhage in the adjacent retina and that if the spastic lesions disappeared with the termination of pregnancy, the blood pressure dropped to normal but where organic vascular lesions remained, the blood pressure was persistently elevated. Corwin and Herrick,[42] Peckham,[43] and other observers, in follow-up studies of women whose pregnancies were complicated by toxemia of pregnancy, have emphasized the causative relationship between toxemia of pregnancy and chronic vascular and renal disease.

In 24 cases in our series, ophthalmoscopic examinations of the retinae were made at the onset and during the course of toxemia. Fifteen of these cases were further studied six weeks after delivery. There were three cases of eclampsia and one of abruptio placentae, and in every case, localized and elongated retinal arterial spasms along with generalized constriction of one or more of the major arterial branches, were seen. On retinal examination of these cases six weeks after confinement, one, an eclamptic, presented a normal retina; the remaining three showed evidence of variations in the caliber of the arteries and increased light reflex over the involved portion of the vessels. No hemorrhages or exudates were found during or following pregnancy. The majority of the spasms and retinal changes occurred within a radius of 2 to 3 disc diameters from the disc.

There were 11 cases of pre-eclampsia and in every case changes in the arterial caliber were seen. These changes varied from occasional localized arteriolar spasms, changeable in location or size from time to time, to extensive constriction of one or more arteries. With persisting and increasing toxemia, the sharply localized

spasms changed to spindle-shaped spasms, which, in turn, elongated until the greater part of the length of the artery was involved. In a few of the more prolonged, advanced, cases of toxemia, it was observed that the entire arterial tree became so involved by generalized constriction that it presented a picture of chronic vascular disease rather than that of true toxemia of pregnancy. If the observer, therefore, views the retinal vascular pattern for the first time, after long-standing toxemia has brought about generalized constriction, he may interpret the picture as one of chronic vascular disease. The greater severity of the toxic symptoms, however, will aid in the diagnosis of advanced toxemia. No hemorrhages or exudates were seen in these cases.

Seven of the 11 pre-eclamptic patients reported for examination six weeks after delivery. Four patients presented normal retinae, but in the remaining 3, the arteries were definitely damaged as was evidenced by persistent variations in arterial caliber, increased light reflex over the constricted portions of the vessels and disturbance in the arteriovenous ratio.

Of the 9 cases showing mild to moderate toxemia, 6 presented localized arteriolar spasms. The remaining 3 showed no demonstrable change, except that suggestive elongated constrictions appeared in one or more branches in 2 of these cases, but promptly receded and disappeared when labor was induced.

Four of the 9 mild to moderately toxic patients returned six weeks after delivery, and the retinae were found to be normal in all cases.

In reviewing the charts of the toxic cases, we were impressed with the fact that the degree of involvement of the retinal arteries closely paralleled the clinical aspects of the toxemia and the behavior of the blood pressure. As the toxemia increased, the sharply localized spasms increased in number, then became spindle-shaped and lengthened until finally the appearance was that of generalized constriction, the arteriovenous ratio changing from a normal of 2 to 3, to a ratio of 1 to 3 or 4. The elongated constrictions generally showed a marked pallor of the vessel wall. As the spasms increased in number and the vessels began to show generalized constriction, there was a progressive rise in blood pressure.

It has been our observation that once the local or spindle-shaped constrictions progress to a state of generalized constriction, the blood pressure is slow to decrease during the puerperium. Herein lies the danger of prolonged or expectant treatment of the more severe toxemias, inasmuch as it may lay the basis for chronic vascular disease.

It will be noted that in all cases of severe toxemia, changes in the caliber of the retinal arteries were consistently found. This is exactly what one would expect to find, since hyperguanidinemia is known to be present in cases of severe toxemia, and the action of guanidine is thought to be on the nerve endings or directly on the muscle of the arteriolar wall. If ophthalmoscopic examination was made a part of the obstetrician's examination in every case of toxemia, the uniformity and consistency of the finding would be amply demonstrated. While dilatation of the pupil is necessary for a thorough study of the retina, much can be learned by simple examination without drops, if the room is darkened. In this way, changes in certain arteries may be followed more closely.

SUMMARY

To summarize, therefore, the foregoing investigations in this series of adolescent primigravidas indicate that toxemia of pregnancy is not only much more frequent in hypothyroid gravidas and in adolescence, but is much more severe, and that emphasis should be placed upon youth rather than nulliparity as a predisposing factor in toxemia of pregnancy. They further show that the accepted relation of high blood cholesterol values to low basal metabolic rates and vice versa, also applies during the state of pregnancy and that when toxemia develops, the thyroid is apparently stimulated to greater activity, and responds in a manner apparently similar to its behavior under the influence of other intoxications, by a sharp rise in the basal metabolic rate.

They further demonstrate that the more severe forms of toxemia of pregnancy are associated with the more acute types of placental infarcts and that as toxemia develops and increases, spasms appear in the retinal arteries and grow more numerous and severe until a state of generalized retinal arterial constriction is produced. The degree of involvement of the retinal arterioles parallels the rise in blood pressure and is probably a measure of the involvement of the arterioles throughout the body.

DISCUSSION

Many theories have been proposed to explain toxemia of pregnancy, but until it is recognized that placental infarction is the probable basic factor, we do not believe that any of these concepts will fit into the picture. A theory is more likely to prove to be correct if it is built up, step by step, by correlation of the outstanding clinical and pathologic manifestations of the disease.

The theory proposed by one of us (R. A. B.) to explain toxemia of pregnancy, had its inception in the clinical observation of the frequent association of the so-called "red infarct" on the surface of the placenta in cases of abruptio placentae. Routine examination of placentas extending over a period of ten years during which several thousand were examined, demonstrated the fact that infarcts of the more acute type were consistently found in cases of pre-eclampsia, eclampsia, and abruptio placentae. It became possible to classify infarcts[8] and correlate them with the severity of the toxemia, so that one might predict the type of infarct which would be found in the placenta; or by examination of an "unknown" placenta, one might state whether the patient was normal or toxic.

Microscopic examination of acute infarcts showed necrotic villi with open intervillous circulation, through which the same maternal blood coursed as between the healthy villi just across the border of the infarction. This finding alone disproved the frequently quoted statement that the infarct was the result of the toxemia and not the cause. Manifestly a hypothetical toxin in the maternal intervillous blood, of sufficient toxicity to cause necrosis, could not have a selective action on a certain group of villi, and be harmless to the villi surrounding the infarct. The presence of thrombi in the villous vessels in the infarcted area indicated that necrosis resulted from interruption of the fetal vessels rather than in the maternal sinuses.

The question then arose, as to the cause of interruption in the villous circulation. The frequent finding of yellow-white deposits of fibrin on the fetal surface of the placenta, beneath the amnion, and the occasional finding of a thick layer of fibrin covering a considerable part of the fetal surface, as in Fig. 5 of the previous article[5] indicated that extravasations of fetal blood frequently occurred on the fetal surface of the placenta and were probably due to rupture of a fetal vessel from the trauma of vigorous fetal movements. It seemed reasonable that from rupture, thrombosis at the site of injury, or embolism, infarction of the dependent placental tissue must have occurred.

A definite predisposing cause of infarction came to be recognized in the discovery of the fact that the medium sized or small placental arteries

occasionally showed a localized accumulation of large transparent cells beneath the endothelium either surrounding the lumen to produce concentric narrowing of the vessel or massed on one side to cause an excentric narrowing of the lumen.[7] These cells were recognized to be morphologically similar to the large fat cells described by Leary[44] in artificially produced cholesterol vascular change in rabbits and also similar to those seen in human coronary thrombosis. It seemed reasonable to believe that in the presence of hypercholesteremia of pregnancy, the trauma of vigorous fetal movements on the unprotected arteries on the fetal surface of the placenta was both a predisposing cause of focal cholesterol vascular change, and also an exciting cause of rupture, thrombosis or embolism after focal cholesterol change had taken place.

Granting the definite association of the more acute types of placental infarcts with toxemia of pregnancy and the occurrence and predisposing influence of cholesterol vascular change and fetal trauma as the etiologic factors in placental infarction, a question still remained as to how the poisonous protein split products of autolysis of the infarct, produced the manifestations of toxemia of pregnancy and convulsions.

It seemed rational to explain the peculiar eclamptogenic nature of autolyzed placental tissue on the basis of its high content of arginine from which guanidine theoretically, might be obtained by a series of oxidation reduction reactions, as shown by Parker.[6] Further work is being done, to show, by chemical proof if possible, that a greater amount of guanidine may be obtained from placentas than from other tissues.

The fact that the placenta contains a higher content of arginine in the fifth, sixth, and seventh months than at full term may be of considerable clinical significance. With liberation of greater amounts of guanidine at this stage, one might expect toxemia to be more fulminating and show higher blood pressure and greater frequency of convulsions. Our clinical impressions bear out this suggestion.

Post-partum hyperguanidinemia may not be sufficient to raise blood pressure or produce convulsions after normal pregnancy, but when superimposed on the pre-existing hyperguanidinemia of pregnancy complicated by toxemia, the combined effect may be sufficient to produce late post-partum convulsions, which are known to occur as late as the seventh to tenth day after delivery and which have always seemed to be a stumbling block to any theory of the cause of eclampsia.

It is altogether possible that this finding explains another phenomenon which is often seen after delivery in patients in whom toxemia has existed for some time late in pregnancy. Following delivery of the patient one expects the blood pressure to fall, but in many cases it rises daily, reaching a maximum level as late as seven to ten days post partum. A marked rise in blood pressure within the first week after delivery, therefore, is not without significance and may indicate the possibility of post-partum eclampsia. It is altogether possible that the physiologic post-partum hyperguanidinemia may explain the headaches which occur so frequently in normal cases the first week following delivery.

The antagonistic effect of liver extract on guanidine may possibly explain some of the paradoxical findings which are seen in those cases of

abruptio placentae associated with toxemia. Except for the greater frequency of the infarction on the maternal surface of the placenta in cases of abruptio placentae, the placental lesions of eclampsia and abruptio placentae are the same. In abruptio placentae, however, there is a definitely increased incidence of shock with sudden fall in blood pressure and often a hemorrhagic tendency, not only in the uterus but elsewhere in the body. Unlike eclampsia, there is very little tendency to convulsions.

Is it possible that abruptio placentae is the expression of a greater degree of liver damage, than takes place in eclampsia, thereby subjecting the patient to liver extract of her own making? The drop in blood pressure, tendency to shock, and hemorrhage and the rarity of convulsions strongly suggest that this is the case.

Certain practical deductions may be made from this study. It is quite apparent that illegitimacy and nulliparity, do not predispose to toxemia of pregnancy on the basis of worry or the mere fact of nulliparity, but rather on account of the fact that these patients are usually adolescent or in early maturity. Since pregnancy in the very young, carries with it a greatly increased danger of toxemia, it would seem that this might well be taken into account, in the question of very early marriage.

Vorzeimer and others[45] advocated more watchful prenatal care for those patients who presented stigmas of endocrine disturbance and low metabolic rate, on account of the increased liability to toxemia. It would seem necessary to supervise adolescent primigravidas in the same watchful manner and for the same reason. The influence of geographic location, early marriage, or diet may have more to do with statistics on maternal mortality in some sections than a supposed inferior quality of prenatal care.

It would seem advisable to determine the basal metabolic rate of each new patient, early in her pregnancy, likewise the blood cholesterol estimation. If these tests indicate hypometabolism, sufficient thyroid extract should be given to bring the basal metabolic rate to a plus reading, without causing over-stimulation. The possible advantage of this treatment is to lower the blood cholesterol and lessen the tendency to cholesterol vascular change in the placental arteries. Should toxemia develop, notwithstanding this measure, further use of thyroid extract would seem to be contraindicated, since the thyroid is already becoming overactive. There is no indication for Lugol's solution, since attention should be directed to termination of the pregnancy, rather than to the overactive thyroid gland.

Although the behavior of the basal metabolism at the onset and during the course of toxemia would appear to furnish another sign of impending toxemia, we do not believe that this or any other test at the present time, is equal to the blood pressure in reliability or simplicity.

CONCLUSIONS

1. Adolescence is an extremely important predisposing cause of toxemia of pregnancy, and is a much more important factor than parity.

2. Adolescent gravidas with basal metabolic rates of plus 10 or more show little or no elevation of blood cholesterol and apparently are not so liable to toxemia.

3. Adolescent gravidas with basal metabolic rates below plus 10, show hypercholesteremia and are increasingly subject to toxemia as the basal metabolic rate decreases.

4. The high incidence of toxemia of pregnancy in cases whose basal metabolic rates are within a range commonly accepted as normal and who show only moderate hypercholesteremia emphasizes the importance of the trauma of fetal movements as the probable predisposing cause of cholesterol vascular change and the exciting cause of thrombosis in the placental arteries.

5. During the course of developing toxemia, there occurs a sharp rise in the basal metabolic rate, associated with a drop in the blood cholesterol.

6. During the puerperium of toxic patients, the basal metabolic rate falls to, or below its former low level and the whole blood cholesterol rises to or above its former high level.

7. By examination of placentas as "unknowns," it is possible to correctly diagnose the occurrence of toxemia during pregnancy in 85 to 90 per cent of the cases.

8. Spasms and constrictions of the retinal vessels are consistently found in all cases of severe toxemia and parallel the severity of toxemia and rise in blood pressure.

9. The high content of arginine in placental tissue is the probable source of hyperguanidinemia in toxemia of pregnancy, through autolysis of acute placental infarcts.

10. Hyperguanidinemia is the probable explanation of vascular spasms and the clinical and pathologic evidences of toxemia of pregnancy.

11. The possibility of preventing cholesterol vascular change in the placental arteries, by administration of adequate doses of thyroid extract during pregnancy, and restriction of cholesterol-containing foods, would seem to be the most effective measures of prevention of toxemia of pregnancy.

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DISCUSSION

DR. J. C. LITZENBERG, Minneapolis, Minn.—I wish to emphasize one point, especially, that is the easy clinical application of the procedures advised. We know the value of prenatal care. This paper adds another valuable method of detecting the probability of toxemia of pregnancy early in pregnancy.

It has been demonstrated by many authors that in normal cases of pregnancy the basal metabolism gradually rises to plus 10 or 15, possibly a protective mechanism. These authors demonstrated that if a woman has a basal metabolism of plus 10 or more she will not develop toxemia, but if the metabolism be low in early pregnancy, 50 per cent or more of the cases will later develop toxemia. So this paper adds a feature of prenatal care, which by a simple method permits dividing our cases of pregnancy into three groups, namely: first, those unlikely to have toxemia; second, those who, probably, may have toxemia; and, third, those who are almost sure to have the toxemia of pregnancy.

DR. LESTER A. WILSON, Charleston, S. C.—With the high incidence of toxemia reported in this paper we can agree. From a series of 1,000 unselected cases in private practice our incidence of toxemia was 20 per cent. Of this number 6.2 were severe enough to necessitate terminating the pregnancy.

In a recent study of 3,909 admissions to our ward service at the Roper Hospital, 9 per cent of the cases were toxic; 2.8 were eclamptic. It is our belief that toxemia occurs more frequently in certain areas of the South than elsewhere.

The evidence presented does not show, in my opinion, satisfactory proof that placental necrosis resulting in hyperguanidinemia is not the result of some other agent or toxin rather than the cause of the toxemia. If trauma from fetal movement is a factor in producing toxemia why has not a picture similar to eclampsia in human beings been demonstrated in animals?

DR. HERMAN W. JOHNSON, Houston, Texas.—In 1927, 1928, and 1929 Dr. H. O. Nicholas, Head of the Department of Biochemistry of Rice Institute, Dr. Robert Johnston, my associate, and I presented papers before the Texas State Medical Association on the amines as the etiologic cause of eclamptic toxemia.

We argued that the source of the toxin was definitely in the placenta, otherwise it would be difficult to explain the following facts: why the presence of a placenta is absolutely necessary to the production of pre-eclamptic toxemia; why symptoms improve when absorption from the placenta ceases with lowered intrauterine pressure, following death of the fetus and with fairly rapid absorption of amniotic fluid; also why improvement follows rupture of the membranes.

We argued that circulatory obstruction in the placenta was necessary for the production of the toxin, and this obstruction is brought about by several important factors: (1) The embryonal nature of the tissue and blood vessels of the placenta

predispose it to apoplexy, obstruction, and trauma from violent fetal movements; (2) The actual circulatory accident is precipitated by factors having to do with increased intra-abdominal pressure. The human female is the only animal that suffers from eclamptic toxemia and about the only thing she does which no other animal does is to maintain the upright position. The other conditions predisposing to circulatory damage in the placenta are all decidedly those of pressure, first pregnancies, twins, polyhydramnion, overweight of babies.

We must give the credit to Young of Edinborough for being the first to insist on the relationship between placental infarction and eclamptic toxemia. He thought the toxic substance a split protein. When the circulatory obstruction takes place, infarction may be small, massive, or diffuse and nondiscernible macroscopically. Deprived of nourishment the placental cells may be then reduced, by the cell ferments, to their amino-acid content. Among the amino-acids possible of formation would be histidin, tyrosin and arginine, because they are present in placental tissue. Dr. Nicholas found that tyrosine represented 4.26 per cent of the dry weight of placenta. It is apparent that these amino-acids formed in the placenta would hardly be toxic even if absorbed rapidly, because the blood stream has a buffer system to dispose of them as indicated by the constancy of its amino-acid nitrogen. If however these amino-acids of the placenta are converted into their respective amines and then absorbed, they are toxic and continue so until deaminized. The amount of tyrosine in even a small area of infarction if converted quickly and absorbed quickly could be lethal. Hanke and Koessler showed that under certain conditions amino-acids were converted into amines by enzymes of numerous strains of *B. coli*, and later found the same faculty was possessed by various strains of *Streptococcus hemolyticus*. To date there are about eighty organisms with this faculty. This explains the increased incidence of toxemia, in pyelitis, late pregnancy when permeability of large bowel mucosa is increased, respiratory epidemics, etc.

Chemical examinations were made when possible of vomitus, blood, urine, and placenta. We thought at first that histamine, the typical endothelial toxin, which secondarily through the adrenals produces a pressor effect, was the offending amine. All examinations were negative for histamine. Examination for tyrosine was then made and in practically all specimens where the toxemia was marked tyramine was found in the vomitus, urine, blood, and placenta. No tests were made for guanidin, as at that time the test was not very conclusive, and, too, guanidine was thought to be much less toxic.

Tyramine chemically and pharmacologically is quite similar to adrenalin and thyroxin. It has a strong pressor base and accounts very well for milder forms of hypertension in late pregnancy; for pre-eclamptic toxemia; and in the allergic individual where capillary spasm is also produced, for eclamptic toxemia. Capillary spasm, edema, and convulsions are probably allergic reactions to the causative amine. Necessarily the question is more involved than this—other amines, liver function, and parathyroid function, may play an important part in what happens to the patient.

A decade has now passed and we still believe that tyramine is the important amine in the causation of toxemia of late pregnancy.

DR. CARL HENRY DAVIS, WILMINGTON, DEL.—At the Dallas, Texas, meeting of the American Medical Association in 1926, I reported the results of my first study on the changes of thyroid function during pregnancy as evidenced by changes in basal metabolism. Contrary to most reports then in the literature it was found that if a woman with a normal thyroid had adequate iodine during pregnancy her basal metabolism remained almost stationary and within normal limits. A group of 16 women who had thyroid hypertrophy all had an elevation of the basal metabolism above normal limits even though they took iodine. In connection with Dr. Colvin's observations it is interesting to note I had four patients in the group studied who had late toxemia of pregnancy; all had low readings and two were below minus 10 per cent late in pregnancy (J. A. M. A. 87: 1004, 1926). In a later series of one hundred consecutive pregnant women seen at my office early in pregnancy, it was found that 33 per cent had a basal metabolic rate below minus 10 per cent (AM. J. OBST. & GYNEC. 30: 570, 1935). This group had both iodine and thyroid medication during pregnancy, but I do not have data to show whether or not any of them de-

veloped evidence of toxemia. However, I am convinced that women who have hypothyroidism are more likely to develop toxemia than normal women, and that with proper medication this possibility may be greatly reduced if not entirely eliminated. For several years I have urged routine determination of the basal metabolism as a part of prenatal care. Adequate treatment with iodine and thyroid medication during pregnancy is the most satisfactory way to meet the thyroid problem, as it greatly reduces the possibility of an abnormal thyroid in the newborn.

DR. JAMES E. DAVIS, ANN ARBOR, MICH.—Krogh, of Copenhagen, some years ago wrote a splendid monograph calling attention to the blood depots of circulation. He pointed out that 45 per cent of the body's blood was at rest under ordinary conditions and that only 55 per cent of the total mass of blood was in circulation. Under conditions that are depressive the depot blood is increased and the metabolic processes in the smaller vessels of the circulatory mechanism are associated with toxicity. If one studies the smaller vessels, especially of the placenta and elsewhere in the body, he will see that primary changes will take place in the walls of the smaller vessels. Attention is called to the placenta being one of the depots most involved in the pathologic processes of this condition. Therefore, it does not seem wise to attach too much importance to the infarcts. There is no satisfactory explanation given that will go far in accounting for all infarcts.

DR. RICHARD PADDOCK, ST. LOUIS, MO.—Since it is not expedient for every one to do basal metabolic rates on all patients, a most valuable substitute is to watch the change in the patient's weight. When the weight of the patient begins to follow an abnormal course, then we are adequately forewarned, that some change in metabolism is impending.

The expression "infarction of the placenta" is a very loose term. It can be compared to the term "cancer of the uterus." It does not tell us exactly where the change takes place or what type of infarction is going on. Observations associating toxemia with changes in the placenta date back as far as antiquity. It was only after the advent of the microscope and the understanding of placental histology, and later placental pathology, that the different types of placental infarction were recognized. The changes in the placenta resulting in infarction are brought about by perhaps three or more different types of changes in the elements present in the placenta.

DR. EVAN SHUTE, LONDON, ONTARIO.—I feel that there is a very real reason to be apprehensive of hypothyroids in pregnancy. Now almost all hypothyroids have high blood estrins. We routinely do blood estrin tests on our pregnant patients when first seen. As you perhaps know, if you inject estrin into animals you will produce a thyroid hypoplasia. Similarly patients who are hypothyroid have difficulty in excreting estrin.

Perhaps vitamin E administered to such patients exerts its effect through the estrin balance in the body and the thyroid. It has been shown by Singer in England that wheat germ oil will produce some hyperplasia of a thyroid which has been previously hypoplastic. We have had quite an experience now in giving vitamin E in the form of wheat germ oil to patients showing incipient toxemia. The results are encouraging.

DR. J. W. KENNEDY, PHILADELPHIA, PA.—In studying the etiology of any special lesion, we must not overlook the help which may come from the study of the physiology and pathology of analogous lesions elsewhere. According to Dr. Colvin in toxemia of pregnancy we are dealing with an infarct and its absorption, causing toxemic effects.

Heyd has called our attention to deaths of unknown origin following surgery of the liver. In all major operations in abdominal surgery there must be some disposition of operative detritus and blood clots, and the liver is the organ which finally disposes of all protein material, as a part of its metabolic function.

May we assume a similarity in the chemical composition of such postoperative clots and that of placenta infarcts? Of course, there is a marked difference in the histopathologic picture seen in both the liver and kidney of patients who have died

from either late or early toxemia of pregnancy, and those suffering from liver deaths of unknown causes. If this static blood incident to either clot formation or infarct were subject to drainage, it is my opinion, toxemia would not result.

We are familiar with the sudden deaths from ectopic pregnancy where necropsy reveals an insufficient amount of intra-abdominal hemorrhage to have caused a fatal issue. It is of little satisfaction to any earnest consideration of a subject for us to dismiss so tragic a death by saying it is due to shock from free blood acting as a foreign body within the abdominal cavity and thus dismiss the harmful consequence in the way of toxemia from absorption of the intra-abdominal blood or clots.

We do know this, that from an extensive experience in vaginal hysterectomy clamp method, where drainage is most efficient and there is no concealed or confined blood clots for absorption, we never find from necropsy lesions of the kidney or liver typical of any kind of toxemia.

DR. W. WAYNE BABCOCK, PHILADELPHIA, PA.—I would like to call attention to the fact that the most common cause of a high basal metabolic rate is a nodular toxic goiter or adenoma of the thyroid, and that the toxic symptoms usually become manifest between the ages of 35 and 45 years. In a large percentage the thyrotoxic basis for the increased metabolism is not diagnosed, for many clinicians associate thyroid disease with a prominent goiter or the staring eyes of the much less common exophthalmic goiter, which usually reaches a recognizable toxic stage between the ages of 25 and 30 years. As pregnancy may activate a dormant adenoma of the thyroid we would expect such activation to be more common in the later years of a woman's fertility, the adenomatous years. As the adenoma may be so small or so far within the chest as not to be felt, I feel that a pregnant woman, toxic and with an excessively high basal metabolic rate should immediately receive iodine or an iodide by mouth or parenterally pending the establishment of the diagnosis.

DR. COLVIN (closing).—Regarding Dr. Kennedy's statement concerning the avoidance of large stumps in pelvic surgery, it does not seem possible that such pedicles of tissue could be the origin of a sufficient quantity of guanidine to cause liver damage, inasmuch as Harding and Fort have already shown that various tissues of the body contain approximately one-half the amount of arginine as found in placental tissue.

As to whether the infarcts are the cause or the effect of toxemia, we emphasize that, contrary to Young's belief, the infarction is on the fetal side of the placenta and is concerned with the etiology of toxemia rather than the result of toxemia. The isolated lesions, thrombosed villous vessels and open intervillous channels in acutely infarcted tissue, as seen microscopically, offer proof of this claim. If the infarct is looked upon as a result of toxemia, why should isolated areas become involved in infarction while the remainder of the placental tissue escapes damage?

We wish to stress the element of fetal trauma as an important factor in the production of placental infarcts. The unprotected fetal circulation on the placental surface is unique. As a rule the organ is situated in the uterus, adjacent to the podalic pole of the fetus, exposing its unprotected vessels to the trauma of movements of the fetal extremities. In normal vessels no damage is done, but in cholesterol damaged vessels the intima is more likely to be broken, followed by thrombosis, embolism, and infarction of the involved tissue.

Talbot has pointed out the deviations in basal metabolism among young women from a geographical standpoint. It is our belief that this deviation from normal, rather than inadequate prenatal care, is one of the factors responsible for the high incidence of toxemia of pregnancy throughout the southern United States.

CLINICAL SYNDROMES REFERABLE TO FAILURE OF OVULATION

With Special Reference to Certain Cases of Sterility and Functional Bleeding

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SO BRILLIANT have been the advances made in our knowledge of the physiology of the female reproductive cycle, and especially of its endocrinology, that we are likely to lose sight of the fact that these cyclical phenomena are of only ancillary importance, and that the central actor in the whole process is the egg itself. To put it another way, the cardinal function of the female genital apparatus is childbearing and not menstruation. As a matter of fact, the actual bleeding of menstruation has a negative significance, for its occurrence is in general indicative of failure of conception.

The chronologic relationship between ovulation and menstruation is now well established, at least in that we know that the egg is not extruded at the time of menstruation, as was once believed, but at some time in the interval, ordinarily about midway between periods, with individual variations as to the exact day. We are still in the dark, however, as regards the hormonal mechanism involved. It can be said, however, chiefly on the basis of studies by Hisaw and his collaborators,[2] that the essential hormones are the gonadotropic principles produced by the anterior lobe, the follicle first maturing under the influence of the follicle-ripening principle, and rupturing only if to this is added a small proportion of the luteinizing principle. With ovulation as with so many other endocrine phenomena we deal with a delicate quantitative balance between hormones, and the evidence indicates that this balance varies in different species and in different animals of the same species. It is not surprising that disturbances of this mechanism may occur, and that ovulation therefore may fail to take place. In such cases it seems that the follicle hormone alone is produced, but for some reason the luteinizing mechanism is not touched off. Whether or not this luteinizing defect is always due to insufficient maturation of the follicle, as some believe, is not certain, though this seems unlikely in view of the fact that the unruptured follicle may continue to grow and to produce excessive amounts of the estrogenic hormone. On the other hand, the evidence indicates quite clearly that luteinization cannot occur unless follicle maturation has advanced to a certain point.

If ovulation fails to occur, the growth of the follicle is sooner or later checked, as we believe, by the reverse inhibitory effect of the follicle

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For lack of space, certain portions of this paper have been omitted.

hormone upon the anterior lobe. More recently the studies of Smith, Smith and Pincus[3] have seemed to suggest that in the explanation of either normal menstrual bleeding or that of the abnormal so-called functional variety, we must consider not only the factor of hormone withdrawal, but also that of changing ratios between the various forms of estrogen. The progesterone found after ovulation is apparently the chief determiner of this changing balance. In the normal cycle it brings about a conversion of estrone into the less active estriol, which therefore shows a relatively high level during the luteal phase of the cycle. On the other hand, a drop in estriol precedes the onset of menstruation, as might be expected because of the regression of corpus luteum function occurring at this time.

The fact that in certain animals, such as the rabbit, the act of coitus is the determiner of ovulation, has led to much discussion as to whether the exciting factor of the pituitary is of nervous or endocrine nature. The recent work of Brooks[4] would seem to indicate that in rabbits the former is the case, the nerve paths reaching the pituitary from the hypothalamus by way of the pituitary stalk. For example, after severance of the stalk 18 rabbits failed to ovulate even though they mated frequently. This question is of some importance in its human connotations in spite of the fact that there is as yet no evidence whatever to support the belief of Grosser and others that copulation may be the direct exciting cause of ovulation. It will be recalled that this is one of the objections which has been urged against the reliability of the Ogino-Knaus doctrine of a "safe period," and the theoretical possibility of at least a vestigial degree of participation of the nervous system even in the human ovulation cannot be denied.

The bleeding of anovulatory cycles may occur with just about the same rhythm as the more common ovulating cycle, and it may be normal in amount and duration. So far as the woman herself is concerned, menstruation may in other words be essentially normal in character and rhythm, even when ovulation is not occurring.

A rather sharp division of opinion has arisen as to whether or not the term menstruation can be properly applied to include periodic bleeding of this nonovulatory type. There are many who insist that only when periodic physiologic uterine bleeding is associated with ovulation and corpus luteum formation, and when the actual bleeding is preceded by characteristic predecidual secretory changes in the endometrium should the term menstruation be employed. It is probably futile to belabor such questions of definition, but to my mind the above definition is a totally unwarranted limitation of the term "menstruation," which has always referred to periodic physiologic uterine bleeding regardless of its hormonal mechanism. For that matter, the term was employed centuries before we had the slightest conception of its mechanism, long before hormones were thought of, and long before ovulation was known to be in any way related to menstruation. In those early days, menstruation was thought of simply as a periodic purging of the woman's blood, the purpose of which was to rid her of supposedly unclean and noxious principles. It is in this sense that the word "menstruous" is

used some seven times in the Bible. Why should a term of such ancient vintage now be restricted to one particular hormonal type, even granting that this is by far the most common? One might almost as well argue that the term childbirth should be applied only when the baby is born by the common vertex mechanism, but not when an unusual or abnormal mechanism is involved, as with a breech or face presentation.

To emphasize how menstruation and ovulation, which most characteristically proceed hand in hand, may in a minority of cases diverge, let us review briefly the development of the menstrual function in the individual woman. On the basis of both histologic and hormonal studies it is known that a certain degree of follicle maturation and estrogenic

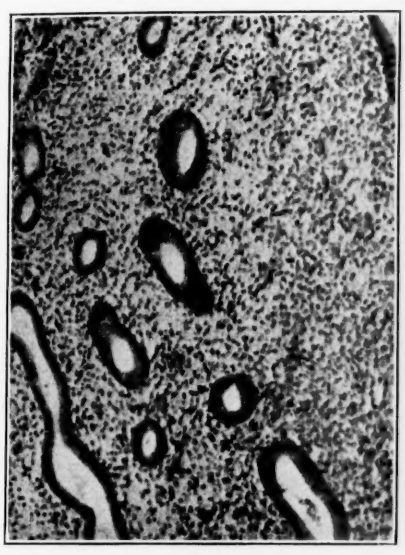

Fig. 1.

Fig. 2.

Fig. 1.—Endometrium obtained by premenstrual biopsy in a girl of 17 years. There is no suggestion of secretory activity, and it may be assumed that ovulation has not occurred.

Fig. 2.—Similar endometrium, also obtained by premenstrual biopsy, in a girl of 14 years.

function begins a considerable time, often several years, before the appearance of the first menstrual period. When estrogenic function reaches a sufficiently high point, the reciprocal influence upon the anterior pituitary brings about periods of regression associated with periodic bleeding, often with no follicular rupture or corpus luteum formation.

This is not a mere speculation, for it is readily demonstrable by the histologic study of the endometrium in young girls. Menstruation in such cases may be more or less irregular for many months, but not infrequently it is of approximately four weeks' type, with a flow which in amount and duration is within normal limits. Opportunities for studying the endometrium in cases of this essentially normal variety are for obvious reasons not numerous, but I have encountered a suf-

ficient number to convince myself that essentially normal menstruation may occur from an endometrium of almost any histologic type. Recently I have performed premenstrual endometrial biopsies upon a group of 6 young patients upon whom some type of surgical procedure was necessary. These patients were of the following ages: 14, 15, 16 (2), 17 (2). In only one of these, a girl of 16, was the typical secretory endometrial picture exhibited, the others showing various degrees of proliferative but non-secretory activity (see Figs. 1 and 2).

Such a small group of patients is of no value in indicating the actual incidence of nonovulatory cycles in the early period of menstrual life, but it does definitely establish the occurrence of such cycles in girls who to all intents and purposes are menstruating normally. I believe that when such observations are multiplied they will reveal that in young patients anovulatory cycles are very common, just as has been shown to be the case in immature monkeys. Moreover, such studies will quite certainly bear out the recent observations of Hisaw and his collaborators, as well as those which many of us have made on our human material, that bleeding can occur from almost any histologic type of endometrium.

Circumstantial evidence along this line is to be found in the studies of Mikulicz and Knausch[5] upon young primigravidas in the Berlin Frauenklinik. These indicate that a considerable number of such young patients, though leading active and unprotected sex lives, failed to conceive for a considerable time, often several years, after the menarche. Such studies are perhaps of limited scientific value, but they are strongly suggestive, in view of the definitely established occurrence of nonovulatory cycles in many young girls.

On the other hand, there is no doubt that in many, and probably the great majority, of girls, ovulation occurs from the first menstrual cycle, and that the very first menstrual bleeding is preceded by a first ovulation. That this must be true is indicated by the occasional occurrence of pregnancy before the appearance of menstruation. Furthermore, the fact is further established by the finding of secretory endometrium in premenstrual biopsy in many young patients. It is futile at the present time to talk of the numerical frequency of ovulatory as compared with anovulatory cycles at this phase of life, or for that matter, at any other phase. The simple fact is that a sufficient amount of accurate data is not yet available in the literature to justify any estimates on this point. It does seem clear, however, that either ovulatory or anovulatory cycles may occur during early menstrual life, and that in any one patient some cycles may be ovulatory and some anovulatory.

Why do some girls ovulate and others not? The answer to this question would at once convey the answer to the query as to what causes ovulation. The riddle is still locked up in the anterior pituitary, though definite progress has been made toward its solution. It seems to have been definitely established that rupture of the follicle alone is not sufficient to ensure luteinization, which can occur only if the follicle ripening process has advanced to a sufficient level.

The factors determining the release from the pituitary of the luteinizing fraction which seems to be indispensable for ovulation are not clear. As I have already mentioned, a sufficient degree of priming with the follicle ripening hormone is apparently not the only essential factor, in view of the failure of ovulation in the most common type of functional bleeding, that in which the follicle persists unruptured though functionally overactive. And yet, as we shall see, the use of anterior pituitary-like principles especially rich in the follicle-ripening principles has been suggested to induce ovulation in nonovulating women. Various theories as to the interplay between the pituitary and ovarian sex hormones have been suggested, but as yet the exact motivating force behind ovulation is a mystery.

As we approach the end of menstrual life, divergence of menstruation and ovulation is again frequently noted, and on this point it is possible to secure definite evidence by the simple method of premenstrual endometrial biopsy, as I have discussed in several previous papers.[6] Here again it is impossible to speak of the numerical incidence of anovulatory cycles, though the now numerous reports on this subject leave no doubt as to their comparative frequency. It is now fully justified to say that while probably the great majority of women ovulate until the end of menstrual life, and sometimes beyond, there are not a few in whom the cycle becomes anovulatory for a variable time before its cessation. It also is true that in many women some cycles are ovulatory, and some nonovulatory, a fact which must be remembered in evaluating the results of any method of treatment aiming to induce ovulation.

Between the two extremes of menstrual life, and therefore during the greater portion of reproductive life, there can be no doubt that the overwhelming majority of cycles are of the characteristic ovulatory type, but even here one finds not infrequent exceptions. It is only when these are intensively searched for that they are revealed, and the stimulus for such a search is commonly the effort to find an explanation for the cause of sterility in cases in which all other factors are apparently eliminable. I have thus far studiously abjured statistics in this discussion, for the study of anovulatory cycles in women at any age has been based chiefly upon the study of that small proportion of women who have been subjected to intensive study because of sterility of obscure causation. Such studies cannot give a true picture of the incidence of this type of cycle among women in general. Even in our sterility cases, only a small subdivision call for studies along this line, for in the great majority some other and perhaps very obvious cause is revealed, such, for example, as deficiency in the male partner, tubal closure, or definite endocrinopathies, to mention only the most important.

In my own private practice I have encountered, during the past three years, 39 cases of sterility of this obscure type, among a total of 142 of all types, in which all the more common factors could apparently be eliminated. This high proportion is to be explained by the fact that a great many of these patients had been previously studied elsewhere, and the more obvious factors, such as male sterility and tubal nonpatency, eliminated. In 19 of the 39 cases endometrial biopsy performed within

a few days before menstruation revealed a non-secretory type of endometrium, showing degrees of proliferative activity varying between pictures corresponding to an early interval phase at one extreme, to a marked Swiss-cheese type of hyperplasia at the other. Some of these patterns are illustrated in Figs. 3 and 4. Some degree of endometrial hyperplasia is the most common picture encountered, being found in 11 of the cases. In all of these cases menstruation was normal or approximately normal, though some showed a tendency to irregular tempo, and in some the menstrual amount was above the average, though not pathologic in the clinical sense.

The ages of these patients varied between 22 and 43. Of 10 patients between 20 and 25 years old 4 showed nonovulatory cycles; the same finding was noted in 4 of 11 between 25 and 30; in 3 of 7 between 30

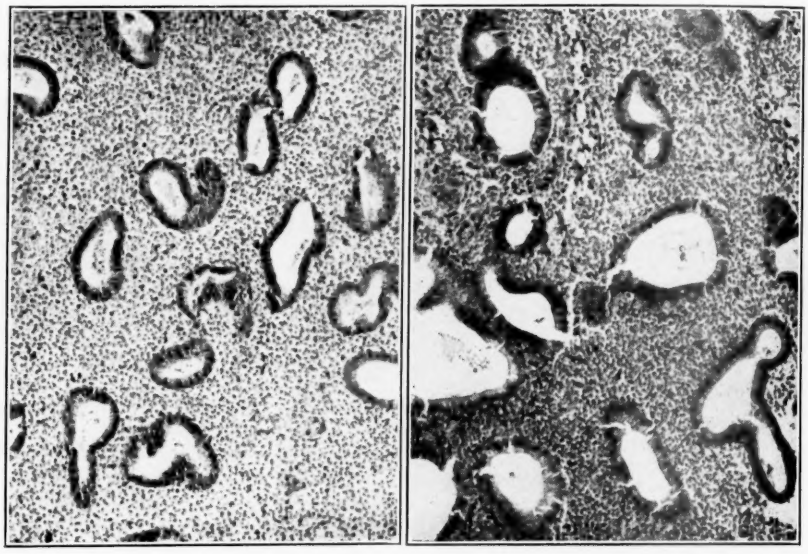

Fig. 3. Fig. 4.

Fig. 3.—Non-secretory premenstrual endometrium in a normally menstruating woman of 39 years. Biopsy three days before expected period.

Fig. 4.—Anovulatory type of premenstrual endometrium in a patient of 40 years. Biopsy day before expected period.

and 35; in 4 of 6 between 35 and 40; and in 4 of 5 between 40 and 45. One thus gets the impression that failure of ovulation is to be borne in mind as a possible cause of sterility, especially in women who are approaching middle life, though it may occur at any age. Sterility in women at a late phase of menstrual life is not by any means an infrequent problem, not only because of the frequency of late marriages, but also because in voluntarily one-child marriages another child is wished for before the menopause, not infrequently because of the death of the first. A number of patients of this type are included in the group mentioned above.

It is not often practical, nor is it usually advisable in the case of women anxious to conceive, to perform endometrial biopsy repeatedly,

because of the great danger of destroying the patient's chances for the particular cycle, should an ovum have been given off and been fertilized. However, from the study of a number of patients on whom I have had opportunity to make such biopsies at intervals, I believe there are some who ovulate with some cycles and not with others, but that more frequently ovulation is likely to be completely in abeyance for considerable periods of time, just as it is in the case of the common type of functional bleeding. The fact that nonovulation may be a sporadic occurrence, however, should make us very conservative in the evaluation of therapeutic measures for this condition.

Even when absence of ovulation is established as the probable cause of sterility, not a great deal can as yet be offered to the patient by way of correcting the defect. Our ignorance of the exact hormonal factors concerned in ovulation explains our present-day floundering in this particular field of organotherapy, as in so many others. Patients of this group characteristically exhibit no other evidences of endocrinopathy, and are usually in good general health. In spite of this, small doses of thyroid are commonly used on more or less empiric grounds. In an effort to induce ovulation, various methods have been used. Among these has been the administration of pregnancy urine preparations, in the hope that, as in the rabbit, these might bring about rupture of the follicles, a hope which has not been fulfilled. This is not surprising in view of the notorious species differences exhibited in this as in other endocrine processes. Only Büttner[7] seems to have noted any histologic effect upon the endometrium from the use of pregnancy urine preparations, combined in some cases with transfused pregnancy blood, reporting secretory changes in a considerable proportion (12 of 16), an observation not supported by others. The administration of a single large dose of estrogenic hormone is believed by some to promote ovulation.

More recently a good many clinics have been experimenting with the use of the gonadotropic principles found in the blood serum of pregnant mares in high concentration at a certain phase of pregnancy, and especially rich in the follicle ripening hormone, as first demonstrated by Cole and Hart[8] in 1930. There is considerable evidence that in such animals as sheep and sows, ovulation is stimulated by this principle and fecundity increased. As yet, however, we know very little as to the effects upon the human ovary, which may respond very differently, if one may judge from the wide species differences in the ovarian response to most other gonadotropic substances.

A very recent publication of Davis and Koff[9] represents a praiseworthy effort to study the problem in human patients, though the results can as yet be considered only suggestive. There are two obvious criticisms of this study as bearing on the possible artificial induction of human ovulation. As the authors themselves say, the majority of their patients were probably having normal ovulatory cycles, so that one would certainly hesitate in ascribing ovulation to the mare serum gonadotropic hormone which was injected intravenously. The results therefore are far less impressive than if a group of patients had been available in whom the nonovulatory type of cycle could be assumed or demon-

strated, as for example, cases of periodic functional hemorrhage associated with a non-secretory type of endometrium. It is of interest to note that 3 of the 36 cases studied by Davis and Koff were actually of this type, and in none of these was any evidence of ovulation found after the gonadotropic injections.

Equally cogent is the objection that must be faced by the authors in their interpretation of the age of the corpora lutea found in the ovaries of their patients, and in their concept of what constitutes evidence of recent ovulation. It is hazardous to base opinions on reproduced photomicrographs, but there will certainly be no general agreement as to the histologic interpretations of the illustrations offered by the authors as evidences of recent ovulation. For example, their Fig. 2, labeled as "showing the general characteristics of a freshly ruptured follicle" and depicting a large corpus, with well-developed antrum partly filled with blood, and with what is apparently a well-formed convoluted lutein zone, would impress many as representing a corpus a good many days old, certainly much older than the period elapsing between injection and operation. Similar comments could be made on other illustrations, my only reason in mentioning this being to stress the uncertainties of conjectures as to the age of corpora lutea on the basis of gross and to some extent also of the histologic pictures.

There are now many "physiologic-minded" gynecologists who have accustomed themselves to careful inspection of the ovaries at operation, in correlation with the cyclical chronology of the patient. There are few, however, who would feel sure of themselves in recognizing mature follicles, which, in my experience, are much less conspicuous than many atretic follicles. The latter, indeed, are more likely to present prominently on the ovarian surface than mature follicles. Likewise, a very early corpus luteum is commonly entirely beneath the surface of the ovary, as the study of histologic sections reveals. Its wall is characteristically crumpled and collapsed, the lumen often being a convoluted slit, though at times more open. In its earliest stages its wall is about as difficult to distinguish from the wall of an unruptured mature follicle as is the predecidual endometrium of the nonpregnant woman from the earliest stages of genuine decidua. Meyer[10] and many others, including myself,[11] have described the characteristics of very early corpora, and the subject calls for no further elaboration here.

It is quite certain that within the next few years we shall have available much more information as to the effect of the gonadotropic substances of mare serum upon both the ovulating and nonovulating human cycles, and as to whether or not it is to be of value in promoting ovulation in the latter group of patients. Certainly the problem calls for investigation, in view of our lack of other effective measures for this condition. The fact that in many non-ovulating cases we are dealing with what we believe to be an already existing relative excess of the follicle ripening hormone is confusing, but need not necessarily inhibit our efforts to determine the effects of administering principles which are so dominantly follicle-ripening as are the mare serum preparations.

In actual practice one must base one's impressions of the value or lack of value of this form of treatment upon other methods than inspection of the ovaries. The occurrence of pregnancy in previously nonovulating patients would be of some value if it were observed with any degree of consistency following such treatment, but there is no evidence whatever on this point as yet. The demonstration of ovulation by endometrial biopsy, in previously nonovulating patients, would likewise have some value, though it could not be considered convincing, for reasons already indicated. Most valuable as evidence would be the production of ovulation and normal menstruation in the group of cases in which failure of ovulation for long periods of time is so characteristic, viz., the functional bleeding cases. Here again we have no evidence of accomplishments as yet.

Finally, attention must be called to the valuable new approach made available through the work of Venning and Browne,[12] who have shown that a reliable index of progesterone activity is obtained through the demonstration of pregnandiol in the urine. That the latter is an excretion product of the corpus luteum hormone now seems well established, and it seems certain that increasing use will be made of this method in the study of cases of endocrinopathic sterility, as well as in those of habitual abortion.

The other important clinical syndrome due to failure of ovulation is the common type of functional uterine bleeding. As a matter of fact this type of bleeding is invariably characterized by sterility, because of this very absence of ovulation. There are other less common varieties of functional bleeding to which this statement would not necessarily apply, such as those due to quantitative deficiency of progesterone, those due to functional deficiency of the uterine musculature, and those attributable to disorders of the vascular apparatus or vasomotor nerves. The most frequent variety, however, is that due to failure of ovulation, with functional persistence of the unruptured follicle for a variable time, and a consequent persistence and excess of estrogenic influence, associated with absence of progesterone.

In this field, as well as in that of endocrinopathic sterility, studies on the pregnandiol content of the urine should prove increasingly useful in separating cases of functional bleeding into those due to failure of ovulation and those due to other factors. The few data as yet available on this point confirm existing impressions as to the common failure of ovulation in these cases, and fortify our reliance upon microscopic examination of the uterine mucosa in the classification of our cases.

The characteristics of the endometrium found in cases of functional bleeding have been described in my previous papers.[13] It is always non-secretory, most frequently exhibits some degree of hyperplasia, but may be of the normal interval type or even atrophic. Hyperplasia of the endometrium is certainly not to be looked upon as a cause of bleeding, for it represents only an exaggerated growth effect produced by estrogen upon the endometrium. The bleeding phases are, in the light of our present knowledge, to be looked upon as due to drops in estrogen level dependent upon the shuttle-cock interplay between the anterior

pituitary and ovarian sex hormones, and possibly also to the changed proportions between estrone and estriol entailed by absence of progesterone, as already discussed.

This is not the place to discuss the clinical aspects of functional bleeding, nor the details of its treatment. In many patients, particularly those in the younger group, there is a definite place for organotherapy. A number of methods have been used with varying success. It is of interest to note that none of these have in the past been directed toward correction of the fundamental abnormality, which is a failure of ovulation dependent upon pituitary dysfunction. First may be mentioned the use of the prolan containing pregnancy urine principles, as suggested by Novak and Hurd[14] in 1931. In our very first paper we pointed out that any beneficial effect of such treatment was not due to a production of luteinization in the ovaries, similar to that produced by prolan in the ovaries of such experimental animals as mice or rats. The fact that the human ovary does not respond in this way has since then been abundantly confirmed not only in our own clinic but also by the studies of Hamblen and Ross,[15] Hamblen and Thomas,[16] Geist[17] and others. The evidence seems conclusive that the pregnancy urine principles never produce follicle stimulation in the human ovary, and that they are not capable of bringing about the extensive luteinization seen in the ovaries of some animals. We are still ignorant of the mechanism of the good results obtained in at least a considerable proportion of cases of functional bleeding from the administration of the anterior pituitary-like substances of pregnancy urine. For that matter we are still in the dark as regards the nature of the relationship which undoubtedly exists between the chorionic hormones and the pituitary sex hormones themselves.

Since corpora lutea are characteristically lacking in the group of functional bleeding cases now under discussion, it is natural that progesterone should have been resorted to in the matter of treatment, now that active preparations of the latter are readily available. My own experience has led me to the belief that the pregnancy urine preparations are more frequently helpful than those of progesterone, and that there is perhaps some principle in pregnancy urine more frequently hemostatic than the hormone progesterone itself.

The most recent organotherapeutic trend in the management of functional bleeding has been in the administration of certain male hormone principles, particularly testosterone propionate. The past year or two has shown an amazing wakening of interest in the study of the effect of androgenic substances upon the female organism, and the literature of the subject is growing by leaps and bounds. While not directly touching on our immediate subject, the effects of androgenic principles in bringing about alteration of sex characters in female animals have been of special interest. Greene and Ivy,[18] for example, were able, by the injection of large amounts of androgenic substance into pregnant rats, to bring about permanent masculinization of genetically female offspring. Such animals exhibited the development of a penis, Cow-

per's glands, and a prostate, while all except the lower portion of the vagina was absent. Even the gonads showed a definite histologic trend toward masculinization.

As more pertinent to our present discussion may be mentioned that various authors have demonstrated the inhibitory effect of androgenic hormone, commonly in the form of testosterone propionate, upon the estrous cycle of rats (Ihrke and D'Amour,[19] Browman[20]), mice (Robson[21]) and monkeys (Zuckerman[22]). More recently Gaines, Salmon and Geist[23] have shown by biopsy studies of normally menstruating women after treatment with testosterone propionate, that there is a disappearance of the secretory phase in the endometrium, with inhibition of the proliferative changes, so that the endometrium may become hypoplastic or atrophic. It seems logical to believe that these effects are brought about, as these authors suggest, through the medium of pituitary inhibition by the male hormone rather than through a direct inhibitory effect upon the ovary or a peripheral effect upon the endometrium, as others have suggested. A similar inhibitory effect upon the vaginal mucosa has been recently described by Schorr, Papanicalaou and Stimmel.[24]

It is not surprising, therefore, that many of us have felt that the now readily available commercial preparations of testosterone might be useful in cases of functional uterine bleeding, in which we often seem to be dealing with a hyperestrous phenomenon. A number of favorable reports have already appeared (Loeser,[25] Geist and others[26]). My own experience, as yet not large, has led me to believe that this plan constitutes a valuable addition to our armamentarium in the treatment of the many cases in which more effective measures are undesirable, chiefly because of the patient's age and the desire for future reproductiveness. The method is much too new to permit of intelligent evaluation, or statistical comparison with other methods of organo-therapy.

SUMMARY

Concerning many of the endocrinologic matters upon which I have merely touched, an enormous literature has developed, but this I have refrained from reviewing in this brief summarizing paper. My purpose has been simply to call attention to the fact that failure of ovulation occurs not infrequently in ostensibly normal women, and that it is the responsible factor in at least a small proportion of sterility cases and in the most frequent variety of functional bleeding.

With reference to the former problem there is after all much analogy between the two sexes. The more cases of sterility I see the more I am impressed with the frequency and importance of the male factor. Complete aspermia is not at all infrequent in men who otherwise seem quite normal, and in whom there is no history of gonorrhea, mumps, or other infections, and in whom the genitourinary specialist finds no evidence of infection of the prostate or seminal vesicles. The same statement can be made as to necrospermia, which likewise is a frequent finding. That such cases, like our anovulatory cases in women, or like those in which defective ova lead to early and perhaps repeated abortion, are of endocrine causation, probably of pituitary source, seems certain. It is important to recognize these abnormalities of ovulation, even though we must await further developments before we can hope to treat them with any hope of consistent success.

The same fundamental defect, a failure of ovulation, is concerned in the most common variety of functional bleeding, and likewise implies a primarily pituitary dysfunction. If we could therapeutically bring about ovulation in such cases, we would be attacking the problem at its source. Instead of this, we must for the present depend on more superficial methods, such as the use of the anterior pituitary-like pregnancy urine principles, progesterone, and the androgenic hormone. A promising field of investigation in the effort to find a means of promoting ovulation in nonovulating women is the study of the effects upon the ovaries of ovulating and nonovulating women of the gonadotropic principles found in the blood serum of pregnant mares.

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DISCUSSION

DR. ROBERT A. ROSS, Durham, N. C.—Dr. Novak's study in the young female recalls the fact that bleeding can occur from any type of endometrium. As a matter of fact Hamblen from our clinic has reported a case of fatal uterine bleeding in a 17-year-old colored girl and the endometrium was atrophic.

Frequent reference to endometrial biopsy material has been made. We find the biopsy forceps indispensable. To give exact information the biopsy should be taken within the first twelve hours of bleeding, and the findings be interpreted as the sum total result of endometriotropic response. It does not allow a segregation of individual factors.

For the past year Hamblen has been making estimates of pregnandiol from a variety of patients. Perusal of his unpublished data is full of information and full of surprises. The appearance of this product in the urine is dependent on several factors. Progesterone is formed by corpora lutea after ovulation, with a definite possibility of its being formed by the luteinized marginal granulosal cells in follicles. (Such changes have been described in previous studies.) The removal of ovaries containing healthy lutein cells results in disappearance of pregnandiol from the urine. The endometrium aids in the alteration of progesterone into pregnandiol and its removal by curettement or hysterectomy results in cessation of excretion. The liver helps in the conjugation of pregnandiol with glucuronic acid and the kidneys excrete sodium pregnandiol glucuronide. When we consider the variables of production, elaboration, utilization, metabolism, and excretion, we see pos-

sibilities of deviation. We also see the need of a method whereby the levels of progesterone or its products in the blood can be estimated. Variations occur in the excretion of this product in women thought to have normal menstrual cycles and the relationship to the onset of menstruation is irregular. The excretion is not continuous throughout the progestation cycle. Immature or markedly hypoplastic endometrium may not be capable of metabolizing progesterone, and it seems reasonable that progesterone must be altered before it can aid in progestational differentiation. This explains the feasibility of sensitizing atrophic endometrium before the use of the active principle of corpus luteum if a progestational reaction is to be obtained. The ability of the endometrium to metabolize intrinsic and injected progesterone may differ.

Even after the progesterone is metabolized there is no assurance that every endometrium will utilize the product for progestational proliferation. The appearance of the pregnandiol complex in the urine may occur without an associated progestational endometrium. Hamblen ascribes these paradoxes in part to a lowered sensitivity or refractivity of the endometrium and leads to the conclusion that the excretion of sodium pregnandiol glucuronide may not be evidence that an endometrium is undergoing progestational proliferation, nor a failure of its excretion that ovarian function is inadequate. Thus bleeding from an estrogenic endometrium may not be "anovulatory" in character. Thus biopsy, pregnandiol determination and possibly the electric potentiometer are all necessary before the diagnosis of this condition can be made.

PROFESSOR CHARLES BURGER, BUDAPEST, HUNGARY.—An inheritance factor as a cause of sterility may exist as a recessive characteristic. In connection with that I would like to call your attention to some experiments on animals. The heterozygotic type of crested canaries and a breed of orange yellow mice, studied by Cueno, carries a so-called lethal gene. This is shown by the fact that among the young of those animals there always dies soon after impregnation of the ovum, the homozygotic, crested or yellow, type. There is a theoretical possibility that this may be true in human beings also. Perhaps in those cases where we see a prolongation of the menstrual cycle, it was really a very early abortion.

DR. NOVAK (closing).—Functional bleeding must be considered essentially as a disorder of ovulation. It seems reasonable to believe that when we know more about the hormonal mechanism of ovulation in the human being, and how to induce ovulation in nonovulating women, we shall likewise have a far more direct and successful method of treating functional bleeding than the more superficial and often unsuccessful endocrine methods now available, through the administration of preparations containing testosterone, progesterone, or prolan.

As regards the value or lack of value of pregnant mare serum in inducing ovulation, I may say that this problem has been extensively studied in monkeys by Dr. Carl Hartman, of the Carnegie Institute of Embryology, who has not as yet published his results, but who has permitted me to quote them here. Monkeys are certainly the ideal animals for experimental study, for they menstruate just as do women, and, like the latter, not infrequently menstruate without ovulating. Moreover, it is far easier to determine the occurrence of anovulatory cycles in monkeys than in the human being, for this can be readily and accurately done by rectal palpation, as Dr. Hartman has shown. In a series of 104 nonovulating monkeys in which pregnant mare serum was injected intravenously in various and often large or repeated dosage, Dr. Hartman noted ovulation in only 7. Even in these I suppose it is difficult to eliminate altogether the ever-present possibility of spontaneous ovulation. These results are anything but impressive, and since no such criticism could be made of the method of study employed in this series as I have made of the study of Davis and Koff, I believe that we may conclude that the value of pregnant mare serum in inducing ovulation still remains to be proved.

THE ETIOLOGY OF OCCIPUT PRESENTATIONS*

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(From the Department of Obstetrics and Gynecology, University of Kansas)

SEVERAL years ago we became interested in the management of occiput posterior and attempted a review of our experience, but soon found that our diagnoses of presentation were frequently unreliable in several respects. Many of the diagnoses had been made by interns and had not been checked by more experienced observers. In several instances, particularly in private patients, the attendant had arrived rather late and, because external rotation was toward the left, had decided that the presentation must have been O.L.A. The younger men, frequently, did not consider the possibility of an occiput posterior, even when, by abdominal examination, the findings pointed strongly in that direction. It very soon became apparent that a much better method of diagnosis, carefully controlled by experienced examiners, would be necessary before any accurate idea of the incidence of the various positions could be developed. Most of the textbooks in the more recent editions had included a statement that occiput posterior was probably more frequent than had been generally supposed. These texts had, in fact, revised their estimates upward from a very small percentage in earlier editions to as much as 25 per cent in the more recent.

In order to arrive at as accurate an idea of the incidence of the various positions as we possibly could, we set up the following plan: (1) That diagnoses of presentation and position should be made as early in labor as possible; (2) that at least two examiners should check one another; (3) that the diagnoses of the intern should not be accepted in any case; and (4) that if the labor had progressed to complete dilatation and the head had descended nearly to the pelvic floor, no diagnosis at all (beyond unclassified cephalic presentation) would be made.

We have tried to follow this plan carefully ever since and we believe we have a more accurate idea of the frequency of the various positions than before. We have not, of course, been able entirely to eliminate errors in diagnosis, but would estimate that the gross error in our present figures is probably not greater than 5 per cent. It should be noted that of the total of 2,282 cases, here reported, 109 are diagnosed under the term "cephalic." This includes patients seen late in labor and those upon whom the diagnosis has not been definitely made, either because of a very large caput or paucity of examinations due to eclampsia or some other inhibiting condition. Several of these patients were thought to have had occipitoposterior presentation, but the diagnosis was not clearly established.

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One hundred seventy-one patients had diagnoses of brow, face, bregma, shoulder, breech or twins, and hence were excluded from this discussion of occiput presentation of a single fetus in utero.

This leaves a total of 2,002 occiput presentations where the diagnosis was carefully made and considered reliable for classification according to position. In each instance, the direction of the sagittal suture and the position of the posterior fontanel have been recorded on the chart early in labor. In the vast majority of these cases, this record has been made previous to 6 cm. dilatation. We have labeled as occiput anterior all cases where the sagittal suture was anterior to, or exactly in, the transverse, but never posterior to that point, and have designated as posterior only those instances where the small fontanel was actually back of the transverse diameter of the pelvis.

Since using this method of diagnosis and plan of classification of position, we have had 863 O.L.A. patients; 649 O.D.P.; 332 O.L.P.; and 158 O.D.A. (total: 2,002 patients). These figures are, in some respects, in quite sharp contrast with even our present ideas of the incidence of the various positions. O.D.A. is, in this series, the least common, instead of the usually quoted O.L.P. Presentation in the left oblique diameter (O.L.P. and O.D.A.) is less common than in the right oblique, as usually stated in the various textbooks. On the basis of these revised figures, it occurred to us that perhaps a more adequate explanation of the etiology of position might be made available.

If no factors other than pure chance were at work, presentation should occur with equal frequency in each of the four quadrants of the mother's pelvis. That other factors are at work has been agreed to by most authors, although some of the explanations offered have not been entirely acceptable.

Beck[1] states that "the smooth, dorsum of the fetal ovoid better fits the anterior wall of the uterus which lies in contact with the abdominal wall." DeLee[2] observes "with the woman in the erect position, the back of the child will naturally occupy the roomy anterior half of the uterus." Schumann[3] says, "with the mother in the erect position and moving about, the fetal back naturally tends to occupy the roomy anterior portion of the uterine cavity, especially if the abdominal walls be slightly relaxed." None of these sound very convincing. On the other hand, Beck[1] says, "the presence of the rectum on the left side tends to make the left oblique diameter somewhat shorter than the right," and Williams (Stander)[4] says, "the occiput is usually found at one or the other extremity of the right oblique diameter of the pelvis, owing to the fact that the left oblique diameter is materially encroached upon at its posterior extremity by the rectum" and Kerr and Ferguson[5] "the left oblique diameter is occupied at its posterior end by the pelvic colon which appreciably diminishes its total space," all of which sound much more plausible.

None of these authors mention the fact that the urinary bladder is, in part, a pelvic organ and that it, when distended, frequently encroaches upon the right anterior aspect of the pelvic inlet. As a matter of fact, photography of the pelvic inlet at autopsy (Figs. 1 and 2) shows that the bladder, when containing as little as 75 c.c. of fluid, really takes up considerable space. No doubt, with the full-term pregnant uterus occupying its usual position in the pelvis, the bladder would be considerably more flattened from before backward than is shown in these.

pictures. Nevertheless, the fact remains that it must, on occasion, act as a considerable hydrostatic wedge. We have concluded that what otherwise might have been an O.D.A. presentation is frequently changed to an O.L.A., or to an O.D.P. This rotation of the head from an O.D.A. presentation to one of the other two, would, it seems, occur more frequently toward the O.L.A. than toward the O.D.P., except in those instances when it had primarily come down with the occiput somewhere near the transverse on the right side.

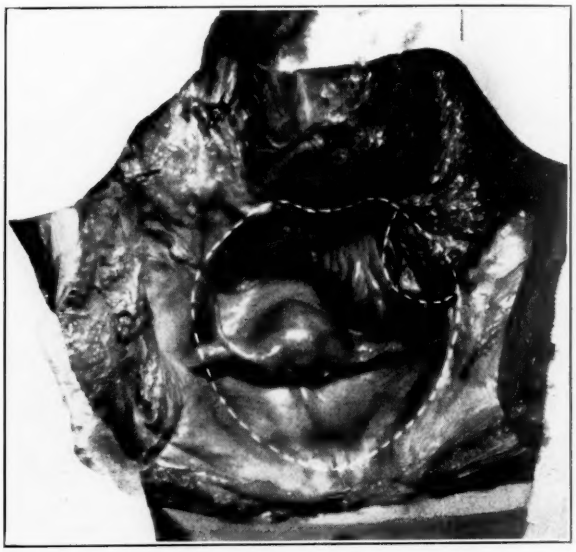

Fig. 1.—Pelvic inlet with bladder empty.

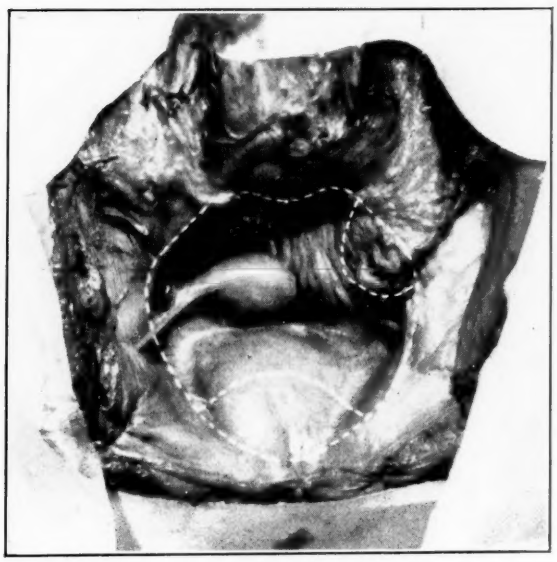

Fig. 2.—Pelvic inlet with 75 c.c. of fluid in bladder.

The pelvic colon, on the other hand, when distended, and thereby changing what was primarily an O.L.P. presentation into something else, would naturally in all cases produce an O.L.A., as it would be rather difficult to push the presenting part past the projecting promontory of the sacrum. We have actually observed one instance where the administration of a one pint enema to a patient early in labor caused rotation from an O.L.P. to an O.L.A.

The relative frequency of the four positions, as above indicated for this series, is quite suggestive when translated to the percentage basis, or to a measure by single digits. They are:

O.D.A.	8 per cent	1
O.L.P.	16 per cent	2
O.D.P.	32 per cent	4
O.L.A.	43 per cent	5+
Total	99 per cent	12+

Pure chance on this basis would cause each position to occur three times in the total of 12 plus. It would seem, on the basis of these two thousand cases that something prevented the occurrence of O.L.P. in one-third of the cases (slightly more often in multiparas and slightly less often in primiparas) and that perhaps all of this one-third had been added to the O.L.A. group. Likewise, one might conclude that some factor may have prevented the occurrence of O.D.A. in two-thirds of the instances where it would have occurred if only governed by pure chance, and that this factor had shifted the position to O.D.P. about one-half the time and to O.L.A. the other half. On this basis, the urinary bladder would seem to be twice as great a prohibitive factor as the pelvic colon against presentation in the left oblique diameter.

SUMMARY

If presentation in the right oblique diameter occurs with much greater frequency than in the left oblique, as is generally agreed by most writers (about seven to one) and has occurred roughly three to one in this series, it would seem that some more adequate explanation than the presence of the pelvic colon in the left posterior quadrant of the pelvis must be offered. The presence of the urinary bladder in the right anterior quadrant convincingly offers this additional explanation and, in fact, the bladder would seem to be a more important factor than the pelvic colon.

It may also be noted that the total of occipitoposterior presentations (981) approximates the total of occipitoanterior presentations (1,021). Possibly, therefore, occiput posterior is not such a serious complication as we have been urged to believe. We hope to discuss this subject soon.

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DISCUSSION

DR. F. J. SCHOENECK, SYRACUSE, N. Y.—We have been interested in this subject at the Syracuse Memorial Hospital because of the growing impression that posterior positions are far more common than ordinarily stated in the textbooks. In this connection I would like to ask Dr. Calkins his reason for including L.O.T. and R.O.T. positions as essentially anterior. These particular positions are usually considered as essentially posterior, especially as far as mechanism is concerned.

In presenting our figures from Memorial Hospital, I must admit that the series is not as carefully controlled as is that of Dr. Calkins. The cases do come, however, from a teaching service and in general have been checked rather systematically. There were 3,999 vaginal deliveries from 1934 to 1937; of these 3,585 are used for the statistics as being the usual vertex presentations.

Using Dr. Calkins' method of including transverse cephalic positions in the anterior group, our percentages are, L.O.A., 44 per cent; R.O.A., 26 per cent; R.O.P., 20 per cent; and L.O.P., 10 per cent.

If we regard the transverse cephalic presentations as essentially posterior the percentages become: L.O.A., 39 per cent; R.O.P. and R.O.T., 24 per cent; R.O.A., 21 per cent; and L.O.P. and L.O.T., 16 per cent.

These figures confirmed our impression of a more frequent incidence of posterior positions in our institution than is ordinarily stated, namely 40 per cent.

That the distended bladder may become a factor in delaying descent and perhaps interfering with rotation is certainly an occasional observation. If the bladder can influence mechanism of labor, it would seem it might also be a factor in determining position.

DR. A. LOUIS DIPPEL, BALTIMORE, MD.—I am wondering what Dr. Calkins' impression is of the actual incidence of occiput transverse positions, which he has grouped with the occipitoanterior positions. Caldwell and Moloy, from an elaborate stereoroentgenologic study of a relatively small series, have shown the importance of transverse positions in the mechanism of engagement, for they have found that transverse positions far exceed those of the oblique positions, the head engaging in occiput transverse in 60 per cent of 200 cases. Plass, from a clinical study, found engagement of the fetal head taking place in the transverse positions in 21.8 per cent of 5,445 deliveries. In our own clinic, we find that engagement always occurs in a transverse position in the markedly contracted rachitic pelves. Furthermore, with the advent of the studies of pelvic architecture, it has become evident that engagement does occasionally take place with the head in direct occiput anterior or direct occiput posterior. Caldwell and Moloy report engagement occurring in direct occiput anterior in 5.5 per cent of 200 cases or 17.7 per cent of 59 cases of anthropoid pelves.

The pelvic colon and the urinary bladder must play some part in the mechanism of engagement. Dr. Calkins has cited the influence of a colon distended by an enema. Occasionally, a distended bladder is known to prevent engagement of the fetal head but with relief of the distention engagement occurs promptly. In the 1920 edition of his textbook, DeLee describes a case in which a distended bladder caused rotation of an originally obliquely anterior to an obliquely posterior position, but with drainage of the bladder the head returned to and engaged in the original occipitoanterior position. The bladder occurs as a right lower abdominal mass with almost the same frequency as dextrorotation of the uterus, statistics showing that this is the position of the uterus in 80 per cent of the cases and Williams stating that the bladder is pushed to the right by rotation of the uterus on its vertical axis in possibly 90 per cent of all pregnant women. If the hydrostatic wedge formed by the urinary bladder were of prime importance in the production of engagement of the fetal head in the right oblique diameter, then the combined percentages of L.O.A. and R.O.P. should approach these figures. This is the case in Dr. Calkins' series, yet he has included occipitotransverse with occipitoanterior positions.

From a stereoroentgenologic study of over 300 pelves, most of which were contracted in at least one diameter of the pelvic inlet, we have had to conclude that in contracted pelves the position of engagement is most often determined by the

shape and size of the pelvic inlet. Frequently, as in the cases of markedly contracted rachitic pelves, accommodation of the fetal head, on account of the marked shortening of the obstetric conjugate, can take place only with the occiput in the transverse position. In contracted pelves, then, we cannot ascribe to the hypothesis that the urinary bladder causes the fetal head to engage most often in one or the other position of the right oblique diameter of the inlet. However, where the pelvic inlet is large, so that accommodation does not have to take place and particularly where the pelvic inlet is circular in shape, the bladder may well act as a hydrostatic wedge to influence the mechanism of engagement.

PROFESSOR CHARLES BURGER, BUDAPEST, HUNGARY.—I agree with Dr. Calkins in general, though I wish to mention another point, that is the physiologic position of the uterus. The pregnant uterus physiologically is not in the midline but falls backward and to the right. Therefore, the left side of the uterus will be more forward. That makes it understandable that O.L.A. and O.D.P. are more frequent than O.L.P. and O.D.A. As the statistics show that O.L.A. is twice as common as O.D.P., therefore it is natural that O.D.A. is less frequent than O.L.P.

I believe that one who especially looks for occiput posterior cases will find them more frequently. But we know also that the majority of these cases show no delay of labor and therefore it has no great practical importance. In the cases where there is a delay we see a prolongation of the first stage and a tardy descent of the head into the pelvic cavity. For the tardy descent of the head I offered four years ago the following explanation:

It is well known that the anterior wall of the bony pelvis or os pubis is much lower than the posterior wall formed by the hollow of the sacrum. As the head traverses the pelvis in the direction of the so-called pelvic axis, all points of the presenting part do not advance an equal distance. The part nearer the pubic arch reaches the outlet sooner than that approaching the sacrum. The situation resembles the bend in a circular race course, where the competitor on the inner side has a shorter distance to travel. In the occipitoanterior positions the small fontanel is in the anterior part of the pelvis and after a descent of only a few centimeters reaches a point deep in the pelvis. On the contrary, if the small fontanel is in the posterior section of the pelvis, or occipitoposterior position, the head will not have engaged in the inlet after traversing the same distance. Obviously, if the small fontanel is in the posterior quadrant of the pelvis the course of labor will be more difficult. The difficulty will be relatively insignificant if uterine action is vigorous or if the head is small in comparison with the pelvic diameters.

DR. GEORGE F. PENDLETON, KANSAS CITY, MO.—I can understand the influence of the bladder and of the rectum in producing a posterior position, but there are other factors. Not only the pelvis but the abdomen may have something to do with the position, and the relaxation of the abdominal wall may be expected to have some effect on position. Last, it would seem to me that the site of the placenta would have a lot to do with position.

DR. CALKINS (closing).—I will try only to answer the questions of why we class the occipitotransverse positions as anterior. There was no attempt to do that. We were interested in a study of occiput posterior and were studiously avoiding the inclusion as an occiput posterior of any case which was, or might be interpreted as, an occiput anterior.

THE INCREASED INCIDENCE OF FETAL ABNORMALITIES IN CASES OF PLACENTA PREVIA*

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(From the Department of Obstetrics and Gynecology, Loyola University Medical School)

IN 1923[10] I wrote a paper in which I tried to point out the relationship between placenta previa and fetal monsters and deformities. Today I should like to present additional evidence that abnormal babies occur more often in cases of placenta previa than otherwise.

In discussing the etiology of monsters it has been customary to distinguish two types. First, the monsters in which the proper conditions to produce them are already in the germ (and are therefore inherited) and second, those deformities which are due to certain external influences which act upon a normal ovum after it is fertilized. In the first group belong such deformities as polydactyly, polymastia, cleft palate and others. Many monsters have been shown to depend on genes. A deformity such as hydrocephalus may be inherited in some individuals and it may be due to external factors in other cases. Furthermore, in some instances monsters may be due to a combination of hereditary and environmental factors. When there is an hereditary tendency to monsters, the environment may determine whether or not a monster will develop in a particular case. However, many embryologists believe that heredity plays only a small role in the etiology of monsters whereas changes in normal eggs brought about by a variety of factors are responsible for most monsters.

Ballantyne says, "There is good reason for believing that malformations and monstrosities are the product of morbid agents acting during the embryonic period." Mall says, "A more careful study of my specimens . . . establishes beyond doubt . . . that all of them (163 pathologic human embryos) are developed from normal ova due to external influences . . . to a condition which I shall term faulty implantation." Mall also says, "Hertwig concludes properly that every human ovum has within it the power to develop into a monster, either anencephalic or otherwise and that it is not due to any abnormal condition of the germ, but to external influences that affect the growth of the egg." Mall pointed out that His was inclined to abandon the theory of germinal origin of pathologic ova altogether. Giacomini, another student of pathologic embryology, emphasized the necessity for studying the form and structure of the decidua in normal as well as pathologic ova for at this point mechanical and nutritive influences must occur which are of prime importance in the production of early pathologic embryos. Likewise, O. Hertwig believed that the power to become monstrous is not inherited but is due to external influences. Van Scheer studied 348 Mongolian idiots and concluded that heredity played no essential part in the origin of these abnormal babies. He believes that a disturbance in the development of the amnion arises from an improper implantation of the ovum in an abnormal uterine mucosa. Malpas investigated 294 malformed fetuses and found that "in the whole series there was only one instance of a

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malformation with a known hereditary bias.'' Hirst says, ''To summarize present knowledge of the probable fundamental causation of monsters, it is fair to state that faulty implantation of the ovum probably due to insufficient preparation of the uterine mucosa by follicular and luteal hormones, plus mechanical and chemical environmental influences must be held accountable rather than inherent germ tendencies.'' Petersen's analysis of his huge statistical data led him to conclude that, ''The observations tend to support the suggestion of Mall that these lethal malformations are due to early environmental disturbance.'' Szendi reported two cases of single ovum twins in which one child was normal but the other was a monster. These monsters were definitely due to intrauterine conditions.

Everyone is familiar with the experimental production of monsters beginning with E. G. St. Hilaire in the early nineteenth century and continuing down to modern times. Particularly noteworthy is the work of Stockard who reduced all abnormal developments to a single factor, namely developmental inhibition or arrest. Stockard said, ''All monsters are the result of the same cause and the type of monster depends upon the time at which the cause was in operation.''

More evidence in support of the importance of environment in the production of deformed embryos comes from a study of tubal pregnancies. Von Winckel believed that fully one-half of the fetuses in ectopic pregnancy were deformed. Mall found that 96 per cent of ova obtained from tubal pregnancies were abnormal. On the other hand, pathologic embryos were present in not more than 7 per cent of all intrauterine pregnancies early and late. On the basis of this vast difference (96 versus 7 per cent), Mall says, ''It seems to me that the argument against the germinal theory of pathologic ova and monsters is overwhelming—pathologic embryos are nothing but young monsters.''

Stockard has shown that single ovum twins as well as all nonhereditary malformations are due to properly timed developmental arrests. (It may be emphasized here that the tendency to produce double ovum twins which are in reality not twins at all, is often hereditary. On the other hand, single ovum twinning is not directly inherited but is the result of immediate environmental influence on the course of development.) Stockard's conclusions are based upon animal experimentation but Arey maintains that these concepts, ''should apply equally well to human abnormalities and twinning provided the ovum is subject to delay before implantation and to arrest afterward. There is ample evidence for both conditions in the tube.'' Arey pointed out that the same conditions that induce or accompany tubal implantation also appear to favor twinning, for tubal twins occur about fifteen times more often than twins in uterine pregnancies.

It is generally agreed that in most cases of ectopic pregnancy the decidual reaction is poorly developed. Since the decidua supplies not only a place for the fertilized ovum to implant itself, but also nourishment for the growing ovum, the high incidence of abnormal embryos and twins in ectopic pregnancies may be due to the insufficient decidual reaction which is present in the tube.

PLACENTA PREVIA

By placenta previa we mean a condition in pregnancy in which part or all of the placenta lies in the isthmus of the uterus. The isthmus of the uterus differs markedly from the corpus anatomically, physiologically and biochemically. The musculature of the isthmus is not as well developed as in the corpus, the endometrium contains fewer glands and there is less stroma than in the body of the uterus. The isthmus has a separate blood supply. During labor it forms the zone of dilatation, whereas the function of the corpus is that of contraction. The isthmus does not react to hormones, hence it does not develop a true premenstrual hypertrophy or a predecidual compacta. Furthermore,

Simon has shown that even in cases where the glands of the isthmus show some dilatation in the premenstrual period, there is no glycogen present or only a small amount. Since glycogen is nourishment for the early ovum its absence may account for the infrequency of embedding of an ovum in the isthmus. Likewise, when a fertilized ovum is implanted in the isthmus or when part of the placenta develops in the isthmus thereby producing a placenta previa, an embryo may develop abnormally because of the deficient decidua, just as occurs in tubal pregnancy. If this supposition is correct there should be more fetal monsters and deformities and twins in cases of placenta previa than in cases of implantation of the placenta in the corpus uteri. Strassmann, Essen-Moeller and Irving have each reported that twins occur much more often in cases of placenta previa than otherwise. Furthermore, Strassmann and Roggenkaemper have each shown that babies associated with placenta previa are relatively underweight for their length. Another difference between placenta previa babies and others is the male:female sex ratio. Wesselink reports that in 980 cases of placenta previa in Holland, the male:female sex ratio was 124:100 instead of the normal 105:100. He believes this is due to the deficient decidual reaction in the lower uterine segment with consequent defective nourishment of the embryo.

CLINICAL DATA

To determine statistically whether or not monsters occur more often in cases of placenta previa, I wrote to many clinics chiefly in the United States but also a few in Canada and Great Britain. I received information from 26 clinics concerning 369,597 labor cases and from 14 additional clinics concerning their placenta previa cases. Among the 369,597 labor cases there were 3,474 fetal deformities, an incidence of 0.94 per cent (Table I).

Mall claimed the incidence of all deformed embryos and fetuses for intrauterine gestations was 7 per cent. However, most of these deformed embryos were expelled spontaneously as miscarriages early in pregnancy. The incidence of fetal monsters at term was only 0.6 per cent. Mall found that "three well-formed monsters are aborted in the early months of pregnancy for every one which goes to the end of pergnancy."

Guttmacher has shown that twins occur more than twice as frequently in abortions as in pregnancies which go to viability. Most likely a frequent cause of spontaneous miscarriage in the early months of gestation is placenta previa. Were these interrupted pregnancies to continue to term the incidence of fetal deformities in all pregnancies but especially in cases of placenta previa would be far greater than it is.

In the 40 clinics from which I obtained data, there were 3,423 cases of placenta previa and among these cases there were 94 fetal monsters, an incidence of 2.75 per cent (Table II). Thus the incidence of abnormal babies was almost three times as high in the placenta previa cases as in the entire 369,597 cases (2.75 versus 0.94 per cent).

I found in the literature seven articles in which the number of deformed babies in large series of placenta previa cases was quoted (Table III). The total number of placenta previa cases in these reports was 1,023 and the number of fetal monsters among these cases was

17. If we add these 1,023 placenta previa cases to the 3,423 cases I collected, the total number of cases of placenta previa analyzed by me amounts to 4,446. The entire number of deformed babies in the combined series amounts to 111. Hence, among the 4,446 cases of placenta previa the incidence of deformed children was 2.5 per cent (Table IV). This figure is between 2½ and 3 times as high as the incidence of fetal deformities in the 369,597 cases.

TABLE I

INSTITUTION	NO. OF LABOR CASES	NO. OF FETAL DEFORMITIES
Philadelphia Midwives (Nicholson)	96,500	192
Chicago Lying-in Hospital	35,179	611
Johns Hopkins Hospital (Manahan)	32,000	224
Elizabeth Steel Magee Hospital (Ziegler)	23,958	305
Edinburgh Royal Maternity (Sturratt)	22,740	198
Margaret Hague Hospital (Cosgrove)	21,433	393
Cook County Hospital	16,242	48
Chicago Maternity Center (Tucker)	14,315	48
Lewis Memorial Hospital—Chicago (Fortin)	13,261	129
Woman's Hospital—Detroit (Daniels)	11,122	176
Lying-in Hospital—New York (Stander)	10,099	287
Woman's Hospital—New York (Barrett)	9,623	161
Royal Victoria Hospital—Montreal (Fraser)	9,194	66
Methodist Episcopal Hospital—Brooklyn (Matthews)	8,617	226
Cedars of Lebanon Hospital (Lazard)	6,514	62
Carney Hospital (Phaneuf)	6,428	10
Stanford Univ. School of Med. (Fluhmann)	6,279	8
Multnomah Hospital (Holman)	5,693	38
Bellevue Hospital (Freed)	4,030	26
University of Southern California (McNeile)	3,779	80
University of Michigan (Miller)	3,447	119
Indianapolis City Hospital (Beckman)	2,500	9
Wesley Hospital—Chicago (Serbin)	2,040	4
M. P. Rucker (Richmond)	1,579	12
University of Wisconsin (Harris)	1,612	22
St. Margarets Hospital—Pittsburgh (Titus)	1,313	20
	369,597	3,474, 0.94 per cent

The incidence of fetal deformities in cases of placenta previa most likely would be much higher than it is were it not for the fact that there are two types of placenta previa. In the first type, the ovum is implanted in the lower part of the body of the uterus and a portion of the placenta grows down into the lower uterine segment. In the second type, the ovum is primarily implanted in the isthmus. In the first group of cases, there is ample nourishment for the growing ovum, hence little chance for the development of a monster. In the second group, however, the decidual reaction is incomplete and hence there is a much greater likelihood for the development of an abnormal fetus. Fortunately the second group is much less common than the first, else there might be a greater incidence of fetal deformities.

In emphasizing the relationship of the lower uterine segment to fetal deformities, I am not unmindful of the fact that the actual total number of monsters in pregnancies situated in the body of the uterus is far

TABLE II

INSTITUTION	NO. OF PLACENTA PREVIA CASES	NO. OF FETAL DEFORMITIES
Edinburgh Royal Maternity (Sturratt)	531	5
London Hospital for Women (Davies)	481	8
Elizabeth Steel Magee Hospital (Ziegler)	247	3
Johns Hopkins Hospital (Manahan)	222	10
Chicago Lying-in Hospital	194	12
Margaret Hague Hospital (Cosgrove)	149	4
Cook County Hospital	140	10
Toronto General Hospital (Scott)	132	7
University of Minnesota (Litzenberg)	100	0
Woman's Hospital—New York (Barrett)	89	2
University of Southern California (McNeile)	80	1
Hospitals of Memphis (Reinberger)	75	2
Woman's Hospital—Detroit (Daniels)	66	1
Cleveland Maternity (Bill)	65	4
Cedar Rapids—Iowa (Brown)	62	2
Evanston Hospital (Smith)	60	1
Lying-in Hospital—New York (Stander)	58	4
University of Michigan (Miller)	56	6
University of Rochester (Wilson)	56	0
Royal Victoria Hospital—Montreal (Fraser)	48	0
Lewis Memorial Hospital—Chicago (Fortin)	47	4
University of Kansas (Calkins)	47	0
Methodist Episcopal Hospital—Brooklyn (Matthews)	45	1
Multnomah Hospital (Holman)	44	0
Cedars of Lebanon Hospital (Lazard)	38	0
Stanford U. Med. School (Fluhmann)	35	0
Louisville City Hospital (McConnell)	34	3
University of Iowa (Plass)	30	0
Richmond, Va. (Rucker)	29	0
Indianapolis City Hospital (Beckman)	27	0
Bellevue Hospital (Freed)	25	1
Sibley Memorial Hospital—Washington (Kotz)	24	0
Chicago Maternity Center (Tucker)	21	2
British Post Graduate School (Moir)	21	1
Wesley Hospital—Chicago (Serbin)	12	0
George Washington University (Kotz)	12	0
University of Wisconsin (Harris)	11	0
St. Margarets Hospital—Pittsburgh (Titus)	10	0
	3,423	94, 2.75 per cent

TABLE III

AUTHOR	CASES OF PLACENTA PREVIA	NO. OF DEFORMITIES
Irving	308	2
Genova	285	5
Arnold	173	3
Siegel	101	3
Lieberman	79	1
Edinburgh Maternity	41	2
Ekas	36	1
	1,023	17

greater than the number of defective babies in the lower uterine segment. This, of course, is due to the fact that corpus pregnancies occur about 1,000 times more frequently than cases of placenta previa (DeLee, Williams). However, whereas abundant and healthy decidua is found in the vast majority of pregnant uteri, there are instances where for one reason or another the decidua is defective. When ova are implanted in such uteri with defective decidua, deformed babies may result. The occurrence of abnormal decidual reaction may explain why women who give birth to monsters frequently have miscarriages, premature labors,

TABLE IV. SUMMARY

Total number of labor cases	369,597	
Number of deformed babies	3,474	
Incidence of deformed babies		0.94 per cent
Total number of placenta previa cases in forty clinics	3,423	
Number of deformed babies	94	
Incidence of deformed babies		2.75 per cent
Total number of placenta previa cases in forty clinics and literature	4,446	
Number of deformed babies	111	
Incidence of deformed babies		2.5 per cent

and stillbirths shortly before and after the birth of abnormal babies. It may also account for the relative sterility which often occurs just before a malformed baby is born because the decidual reaction may have been insufficient to permit implantation or development of a fertilized ovum. Furthermore, defective decidua may be responsible for the repetition of the same or different types of malformed babies in the same woman, because the abnormal decidua may be present in repeated gestations. Defective children occur much more often in women past forty years of age than in young women. This may be due to the fact that many women who reach forty years of age have gone through a number of full-term pregnancies, miscarriages, and perhaps intrauterine manipulations, such as curettements, manual removal of the placenta, and so on, any or all of which may have resulted in a localized or generalized disturbance in the endometrium.

These ideas are contrary to the belief of Murphy who said, "Reproductive inefficiency was indicated by (a) the long period of relative sterility frequently observed immediately preceding the birth of the malformed child, (b) the nearness of miscarriages, premature births and stillbirths to the malformation pregnancy, (c) the high incidence of malformed offspring born to older mothers, and (d) the increased frequency of congenital defects among brothers and sisters. Since these evidences of reproductive weakness, in very many cases, operated over a period of years, it seems likely that their origins rested upon defects within the germ cells, rather than upon abnormality in the environment."

In support of my contentions and opposed to Murphy are the statements of the embryologists and others quoted in the first part of this present paper and also the following quotations.

Malpas says, "The frequency with which a given malformation was followed later by another type of malformation appeared to show from another standpoint that most of the malformations dealt with could not be due to the action of specific

groups of genetic factors and reinforced the view that they are mostly attributable to the interplay of environmental factors.'' Van der Scheer says, ''In mothers of Mongolian idiots there must be an inhibiting factor of progenitor, the origin of which supposedly must be ascribed to an affliction of the uterus or the uterine mucosa. . . . The cause must be found in the mother because in families with Mongolian idiots there are many miscarriages, fetal deaths, and monsters and there is a long interval between the Mongolian idiot and the previous birth of a live child. The Mongolian idiot is not only often the last born but also a late comer.'' Greig in discussing localized congenital defects of the scalp says, ''Moreover heredity is not a factor, though more than one child in the same family may be affected.''

The 4,446 cases of placenta previa may seem to be a small number of cases on which to base conclusions but when we realize that placenta previa occurs approximately once in a thousand labor cases in general practice, the 4,446 cases represent about 4,000,000 cases.

In some clinics the difference between the incidence of monsters in the cases of placenta previa and all the obstetric cases is striking. For example in the old Chicago Lying-in Hospital with which I was associated, there were 35,179 babies born from July 1, 1918 to June 1, 1931, when the hospital was closed. There were 611 fetal monsters in this series, an incidence of 1.7 per cent. On the other hand, among the 194 cases of placenta previa observed in this institution during the same time there were 12 monsters, an incidence of 6.2 per cent. All of the monsters were dead on delivery or died shortly afterward. There were six babies with anencephalus, two with spina bifida, two with eventration of the viscera, one with hydrocephalus, and one with scleroderma neonatorum (Hospital Nos. 11421, 17158, 20409, 24377, 24997, 26695, 58706, 58771, 63991, 66662, 70710, 79799).

The increased frequency of fetal monsters in cases of placenta previa has more than academic interest. First, dangerous and even fatal bleeding may result from placenta previa associated with a hydrocephalus if the latter is not recognized and delivery is forced through the vagina. Second, more and more cesarean sections are being performed throughout the world for placenta previa. It is most uncomfortable to deliver an unrecognized fetal monster by cesarean section, especially if the abdominal route was urged by the physician in order to secure a live baby. Fortunately, in a large proportion of cases of placenta previa, it is possible to detect fetal monsters in utero, if not by physical then by x-ray examination.

In the paper which I wrote on this subject in 1923, I found that 12 of the 21 monsters mentioned in that paper had cranial defects. In my present data I have knowledge of the type of deformity in 67 cases. There were 19 babies with anencephalus, 7 with hydrocephalus and 10 with spina bifida. The anencephalic and hydrocephalic babies can often be detected by physical examination but certainly by means of roentgen ray pictures. Furthermore, as I suggested in 1923, spina bifida may also be detected on x-ray plates if this anomaly is specifically looked for. Hence, approximately half of the monsters associated with placenta previa can be determined before delivery.

The practical lesson, therefore, is that we should bear in mind the increased frequency of fetal deformities in cases of placenta previa and

take an x-ray picture of such a patient. By this means many fetal monsters will be found which otherwise would have been overlooked. In most of these cases conservative means of delivery will be employed. In some cases, however, cesarean section will be the safest treatment for the mother notwithstanding the presence of a monstrosity.

SUMMARY

In this paper I have attempted to show that fetal monsters and deformities occur more frequently in cases of placenta previa than otherwise. Evidence has been presented from embryologists and others to show the great role played by environment in the etiology of monsters. Clinical data to support this are obtained from the very high incidence of malformed embryos and twins in cases of tubal pregnancy where the decidual reaction is only slightly developed. Likewise, it is pointed out that the decidual reaction in the isthmus of the uterus is poorly developed and that this plays a role in the causation of abnormal fetuses in cases of placenta previa. I collected data covering 369,597 labor cases and found that whereas the incidence of fetal monsters was 0.94 per cent for the entire group, the frequency of fetal deformities in the 3,423 cases of placenta previa in essentially the same group was 2.75 per cent. If to these 3,423 cases are added 1,023 cases of placenta previa which I collected from the literature, the incidence of fetal monsters and deformities for the entire group of 4,446 cases of placenta previa (representing approximately 4 million obstetric cases) was 2.5 per cent as contrasted with 0.94 per cent for all obstetric cases.

In approximately half of all the abnormal fetuses associated with placenta previa, the deformity consisted of defects which can easily be recognized by means of x-ray pictures. Hence, in every case of placenta previa an x-ray picture should be taken. The detection of fetal monsters will usually lead to conservative treatment although cesarean section will have to be employed in some cases in spite of the fetal abnormality.

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DISCUSSION

DR. R. M. H. POWER, MONTREAL, QUE.—Environment in relation to the production of monsters must be regarded from the angle of "soil and nutrition"; these are really synonymous terms and are under endocrine control. The endometrium in its secretory phase is the result of endocrine stimuli, and represents the total of endocrine synchronization for that particular month, i.e., the united efforts of the pituitary, thyroid, and the ovary. The influence of imperfect nidation may affect the whole after life of the fetus, and nidation depends upon two factors. First, the ability of the trophoblast to open up maternal sinuses. Second, the susceptibility of the maternal tissues to be opened up. This susceptibility depends upon estrogenic and luteal factors. Therefore, all environmental fetal deformities must trace their origin to one or both of these factors.

Not all portions of the endometrium are affected to the same degree at the same time; thus we may find side by side in the same endometrium, as shown by my slide, advanced stages of preparation, with other areas of decided lack of preparation.

The results of animal experimentation should apply to human abnormalities. A student of animal husbandry recently stated, "Over 98 per cent of hens' eggs are normal, and if properly fertilized will generate a normal chick if circumstances of environment are normal." We must realize from the above statement, that the great majority of teratomatous growths are due to faulty preparation of the soil.

Stockard and others have shown that a reduplication of embryonic parts, may be brought about experimentally by a temporary arrest of embryonic development at a critical growth period. When a growing apical bud of a twig is arrested in development by pinching off or other methods, dichotomous growth occurs and as a result the two adjacent axillary buds, quiescent during the supremacy of the apical bud, begin to develop twin branches. Similarly the same author has produced a reduplication of parts and marked degrees of twinning in trout embryos, by arresting the development at a critical growth period.

DR. J. K. QUIGLEY, ROCHESTER, N. Y.—Dr. Greenhill has made out a strong case for a greater frequency of fetal deformities in the cases of placenta previa. The reason he advances is very plausible, namely faulty implantation due to imperfect decidual reaction which is more common in case of placentation in the lower uterine segment.

Dr. Greenhill's estimate of 2.5 per cent frequency in placenta previa as against 1 per cent in all pregnancies, while it means that this frequency is two and one-half times, nevertheless means that 97½ per cent of babies born to mothers with placenta previa do not have congenital deformities and abnormalities, so that from a practical standpoint it is not of great importance and I do not believe it sufficient to demand x-ray examination of all cases of placenta previa subjected to cesarean section.

If this form of delivery offers the better prognosis for the mother in some cases, particularly in placenta previa in the primipara and in cases of the central or complete variety, I would not be deterred from this course in the interest of the mother even with a 2.5 per cent chance of obtaining an anencephalic monster any more than I would hesitate to deliver by the abdominal route the occasional case of ablatio with the knowledge that the child had perished, if I thought the chances for the mother were better than by delivery through the pelvis.

A review of the records of the Rochester General Hospital since 1926 revealed 71 cases of placenta previa and in none of these were any congenital deformities found.

There is an interesting parallel in the correlation between anencephalic monsters and hydramnios, acute and chronic. Inasmuch as the cause of hydramnios has never been satisfactorily established, the association of these two conditions is not as easily explained as is the coexistence of placenta previa and fetal deformities. This association of hydramnios and deformities I believe to be much higher than 2.5 per cent.

DR. EVAN SHUTE, LONDON, CANADA.—A good placental foundation ordinarily appears to depend upon the balance in the maternal organism between the invasive qualities of the chorion and the powers resisting chorionic aggression (to borrow Dr. Montgomery's picturesque term). Vitamin E appears to favor villous penetration of the uterine wall and estrogens to resist it. Therefore it is interesting to speculate upon just what is the effect of vitamin E on the origin of monsters.

Recently I had occasion to collect the data in the literature on the fetuses delivered after threatened abortion had been successfully controlled until at least the fifth month by means of vitamin E or its cousinly hormone, progesterone. Of 443 patients so treated only 2 per cent expelled deformed fetuses. If the idea so generally held—viz., that most aborting fetuses are defectives—be true, one can scarcely escape the conclusion that vitamin E and progesterone may actually facilitate a completion of the inadequate development of certain types of defectives if given in time.

In this connection it is interesting to recall Peterson's observation that very few abnormal fetuses are conceived in Chicago in the months of July, August, and September each year. Although this does not appear to be borne out in Philadelphia, according to Murphy's intensive survey, it is true for our part of Western Ontario. As it is in these months that most vitamin E is available in green diets, there may be a correlation between E deficiency and the conception of anomalous fetuses. Hence the biologic significance of such established folk customs as June weddings.

Moreover Peterson's map of the United States showed that the incidence of abnormalities decreased as one went toward the south. Peterson held that barometric pressure was the significant factor in this phenomenon, but I would suggest that dietary variation was the more probable cause.

The problem is not easy to settle experimentally, since such experimental animals as rats, at least, appear to be too well integrated somatically for any disruptive influence of an E-deficient diet to be revealed. However, I have found two hydrocephalic young in the litters of rats on E-low diets and the occurrence of hydrocephalics and cretins in such litters has also been reported by Barrie in England. Possibly more highly organized forms such as man may more easily display a greater variety of response to such vitamin deficiency.

At present we are trying to collect data on women whose only previous conceptions have all ended in the birth of defectives, and whom we can treat with vitamin E from the beginning of later pregnancies. We have only 4 such cases to date, of whom 3 have completed their pregnancies and had normal children. Such a series when much larger may prove significant.

DR. GREENHILL (closing).—Cesarean section will often have to be done notwithstanding a monstrosity because this operation is usually performed for the sake of the mother and not for the child. In cases of partial placenta previa, delivery through the vagina should be carried out when there is knowledge of a deformed baby.

About eighteen years ago while doing some work at the Carnegie Institute in Baltimore with Dr. Streeter, I had an opportunity to learn a good deal about embryos and young fetuses. A relatively large proportion of fetuses expelled spontaneously were found to be abnormal. Because of this knowledge I have always been hesitant about using progesterone in cases of threatened abortion for fear that full-term monstrosities might result. However Shute's information about the 344 cases of threatened abortion with only a 2 per cent incidence of fetal monsters is remarkable. Undoubtedly vitamin E must have played some part.

MATERNAL AND FETAL EXPECTATIONS WITH MULTIPLE PREGNANCY*

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THIS study is offered for three reasons: first, as response to aroused public interest in plural births due to survival of several recent American† and two British‡ quadruplets, and of course the Canadian Dionne quintuplets, to indicate what may reasonably be expected from the occurrence of multiple pregnancy; second, to show that the accident of more than one birth at a single confinement should be anything but a matter of the usual amazement and chagrin to the physician, astonishment and dismay to the parents and amusement to everybody else; and third, to offer personal comments on toxemia of pregnancy as seen in twins and triplets.

The material presented is a brief summary of the literature concerned with unusual complications seen in plural births, as well as leading articles bearing upon our statistics, which are derived from 223,394 total births beyond sixteen weeks' gestation in the City of Philadelphia in the seven years from 1931 to 1937 inclusive, as obtained from the Municipal Bureau of Vital Statistics. From these are obtained through the Philadelphia Maternal Mortality Committee (Philip F. Williams, M.D., Chairman) the plural births among 1,469 puerperal deaths from all causes as well as 835 deaths excluding those associated with abortion, miscarriage and ectopic gestation. To these groups are added detailed progress of 3 sets of triplets and 219 pairs of twins out of 19,463 total births beyond twenty weeks' gestation in the Philadelphia Lying-in Hospital from July 1, 1929, to June 30, 1938; 1 set of triplets and 60 pairs of twins out of 5,483 births in the Maternity Department of the Hospital of the University of Pennsylvania from 1931 to 1937 inclusive, and a recent "experimental" group comprising one set of triplets and 26 pairs of twins from the last 2,000 births in the Preston Retreat, Philadelphia.

The scope of the study does not include speculation on the cause or mechanism of twinning or on the accuracy of reported habitual litters as evaluated by Greulich;[1] or on differentiation and biologic differences and relative frequency of single and double ovum twins, race, recurrence and age, so well described by Guttmacher,[2] but is concerned chiefly with results seen in plural births.

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*Read, by invitation, at the Fifty-First Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, White Sulphur Springs, W. Va., September 22 to 24, 1938.

†Mullins, mixed, aged 1 year, Porter, Okla.; Kasper, mixed, aged 2½ yrs., Passaic, New Jersey; Schense, mixed, aged 7 yr., Aberdeen, S. D.; Morlok, females, aged 8 yr., Lansing, Mich.; Perricone, males, aged 9 yr., Beaumont, Texas; Keyes, females, aged 23 yr., Hollis, Okla.

‡Taylor, mixed, aged 3 months; Mites, aged 3 years.

CITY OF PHILADELPHIA STATISTICS

Maternal Results.—In this large series, in addition to giving the maternal death rate from all puerperal causes, we added an additional rate obtained by deducting deaths associated with abortion, miscarriage, and ectopic gestation for comparison with the twin birth death rate over 16 to 20 weeks' gestation. This was done because many multiple pregnancy miscarriages are overlooked, and because the literature shows only 65 unilateral and 43 simultaneous bilateral ectopic twin pregnancies (Falk and Blinick,[3] Levine,[4] Pudney,[5] Ferguson,[6] Siegler,[7] Lull[8]). It is apparent from

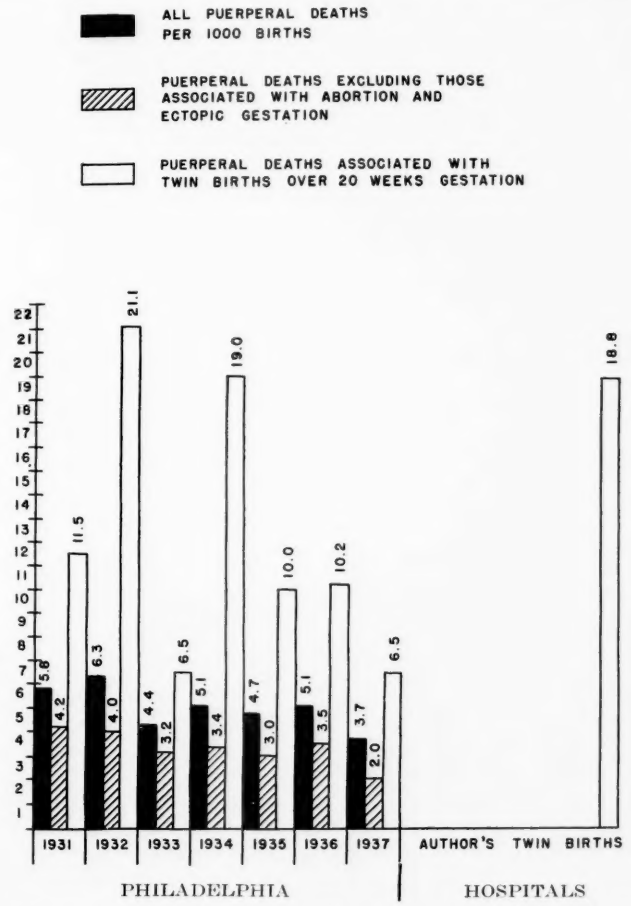

Fig. 1.—Maternal mortality rates in Philadelphia during the last seven years, showing an average of 1.21 per cent for twin births, 0.50 per cent for all puerperal deaths, and 0.33 per cent excluding abortions and ectopic gestations, compared to 1.88 per cent for 279 twin births in the Lying-in and University of Pennsylvania Hospitals.

Fig. 1 that the average maternal death rate (1.21 per cent) associated with plural births over sixteen weeks' gestation, during the last seven years, was three times the average rate (0.50 per cent) for the total puerperal deaths and over four times as great as the average rate (0.33 per cent) for maternal deaths excluding abortion, miscarriage, and ectopic gestation. At this point, it may be stated that Philadelphia experienced no quadruplets over 16 weeks' development, but from the three years 1934 to 1936, inclusive, there were seven known triplet births[9] (1:13,253) and in the remaining four years, 16 calculated (1:8,000) additional, but there were no maternal deaths associated with these 23 triplet births.

Splitting up the twin deaths according to Fig. 2 shows that, whereas the normal incidence of viable twin births averages under 1:90 (1:100+ in our Philadelphia series), the frequency was doubled in the septic and cardiac deaths, quadrupled in the late gestational toxemic, and increased to the amazing frequency of 1:18 in the postpartum hemorrhage fatalities. It is obvious therefore that in spite of the fact that in Philadelphia 80 per cent of all patients to be confined are hospitalized, each woman with multiple pregnancy assumes risk sufficiently great as to require extraordinary precautions suggested later.

Infant Results.—Only the general stillbirth (over 16 to 20 weeks) rates and the neonatal death (over 28 weeks or 1,500 gm.) rates for the years 1931 to 1937 inclusive (Fig. 2) can be presented for the entire city of Philadelphia, since the Still-

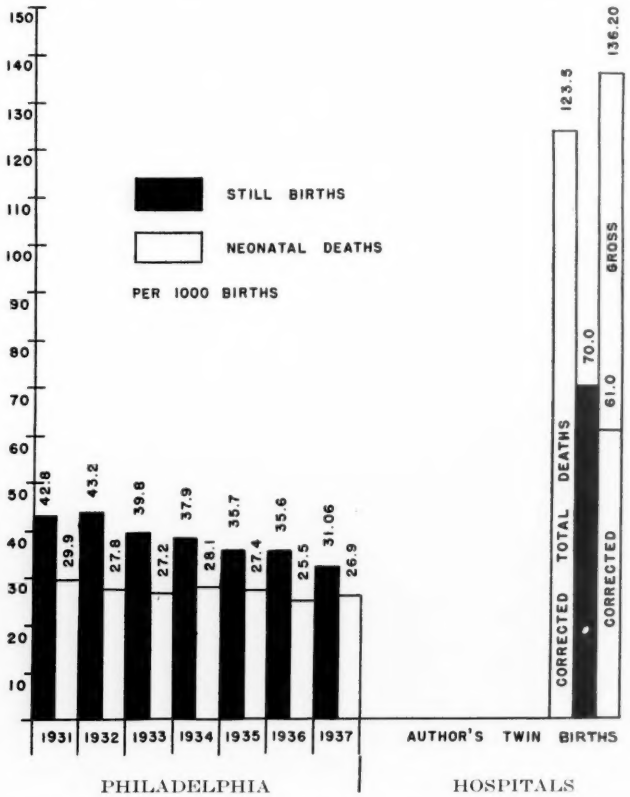

Fig. 2.—Comparison of gross stillbirths and neonatal deaths over sixteen weeks in Philadelphia with rates among 558 twins in the Lying-in and University of Pennsylvania Hospitals.

birth Committee of the Philadelphia Obstetrical Society (chairman, Thaddeus Montgomery, M.D.) and the Neonatal Death Committee of the Department of Health (chairman, Ralph Tyson, M.D.) are of recent origin and have not yet reported causes of their respective deaths. The above rates, like the general maternal rates, show a gradual decline with a seven-year average of 3.8 per cent for stillbirths, and 2.75 per cent for neonatal deaths (total 6.55 per cent), which is roughly one-half the respective rates (gross 7.0 per cent and 13.62 per cent; corrected 6.27 per cent and 6.1 per cent) among 558 twins in the author's hospital series. The latter, totaling 12.37 per cent (corrected), show a reversal of the two types, indicating that prematurity is of greater importance in the postnatal than in the natal period of the infant's existence.

THE LYING-IN, UNIVERSITY OF PENNSYLVANIA AND PRESTON RETREAT HOSPITAL SERIES

Since there were but five instances of triplets, these may be disposed of briefly at this point according to a recent report:[10] toxemia in one mother, post-partum hemorrhage in another, and severe endometritis in a third, but all labors and deliveries easy, due to marked prematurity in each case. One infant was stillborn, four died within a short time and probably the sixth. Since that report, one additional set of syphilitic triplets in the twenty-sixth week of gestation has been confined as an emergency undiagnosed case in the Lying-in Hospital without dystocia or other complications, delivering spontaneously with only twenty-five minutes between infants which were all females and weighed 1 pound 4¾ ounces; 1 pound 4¾ ounces, and 1 pound 4 ounces, all of whom died in a few hours, and combined with the above triplets yield an infant mortality of over 50 per cent.

Progress of twin pregnancy and infants from the first two hospital services, representing 95 per cent registered confinements, are combined and will be described under five headings, namely: pregnancy, labor, delivery, puerperium, and infant.

1. *Pregnancy.*—Among 279 double pregnancies of twenty weeks' gestation or over, there were but 40 primigravidas, the average being gravida 3.8. The duration of pregnancy averaged 35.4 weeks from the first day of the last period, which partly accounts for the fact that only 99 duplications were diagnosed before labor, 20 in labor and 160 or the majority as late as birth. The earliest diagnosed case was that of twins in one horn of a double uterus at thirteen weeks by the author by means of double ballottement and relatively increased urinary anterior pituitary-like excretion. Roentgenography confirmed the diagnosis in 58 cases, proved the only means of diagnosis in 24, was not utilized at all in the great majority or 195, and was erroneous in 2 of the pregnancies, which were classified as: private 34; registered ward 219; registered student out-service 10; and emergency or unregistered 15 (5.4 per cent).

Complications.—Excess weight was frequent, the greatest amounting to 70 pounds (200 to 270 pounds), which according to Matthews[11] when over 200 pounds predisposes to excess kidney, liver, and heart stress, prolonged labor in the majority, some type of complication in 75 per cent, and malposition in 26 per cent of all such cases. Toxemia appeared 37 times as pre-eclampsia (14 quite "mild," and 2 superimposed on nephritis), 3 times as eclampsia, and only 7 times as hyperemesis. If to the mild pre-eclamptics may be added 12 instances of considerable edema only, we obtain a picture simulating low reserve kidney (Stander's[12] temporary disorder distinct from all nephritides, not distinguishable from "mild pre-eclampsia," featured by slight hypertension and albuminuria and occasional slight edema in young nulliparas, and recurring in only one-half of subsequent pregnancies), which this author attributes to the usual decided abdominal tension common to both first and multiple pregnancies, and resulting probably in either renal ischemia or ureteral distortion. This theory is further suggested by the fact that from 40 single viable pregnancies subsequent to twin births reported in our series of whom 8 had experienced toxemia, only 3 showed recurrent toxemia.

On the other hand, if lateral ureteral pressure, deviation or other obstruction be related to late gestational toxemia, it should be especially apparent in multiple pregnancies, yet only 4 of our 279 twins showed obvious ureteral pain and/or infection. This is neither in agreement with original data obtained by the author in 1929,[13] when from many cystoscopic investigations in 2,101 pregnancies appeared 140 (6.6 per cent) cases of proved pyelitis, mostly of the infected hydronephrotic group, and 23 cases of extreme simple hydronephrosis both in much greater proportion among 44 cases of hyperemesis and 232 cases of late gestational toxemia than among the normal pregnancies; nor in agreement with Peter's and Zimmerman's[25] later data on the relation of pyelitis to toxemia of pregnancy. From this we concluded that ureteral-renal embarrassment of some sort including distal ureteral congestion and/or edema was related to gestational toxemia, and having found extreme tempo-

rary bilateral hydronephrosis and *relatively* normal estrogen and anterior pituitary-like excretion[26] in a triple pregnancy complicated by very mild late gestational toxemia at thirty-eight weeks,[9] we continue in this belief, discounting the infrequency of ureteral symptoms in the present twin series on the basis of lack of present cystoscopic facilities maintained in and by the two maternity departments concerned. A final comment on the common edema of late twin pregnancy is the significance of change of blood volume which is increased 26 per cent in normal single late pregnancy[14] and greatest of all in twin pregnancy,[15] all of the aforementioned ideas being apparently opposed to but not incompatible with the generally accepted general-arteriolar-spasm mechanism in late gestational toxemia.[16]

Syphilis played its usual part, affecting 17 or 6.1 per cent of the mothers; severe cardiac deficiency affected 14, while placenta previa and partial abruptio placentae endangered, respectively, 5 and 3 pregnancies, yet there were no prenatal deaths.

2. *Labor.*—Labor began and continued spontaneously towards the second births in 193 of the cases; medical induction was utilized 24 times, and failed only 9 times. Excluding podalic version, the membranes of the first sac were artificially ruptured 14 times, of the second 45 times; and surgical induction was required only 4 times. Only 27 instances of dystocia were noted, with an average duration of 23.4 hours in such cases. In spite of frequent polyhydramnios and malposition, prolapsed umbilical cord was noted only once before birth of the first twin.

Analgesia in the form of morphine sulphate was given 46 times, the maximum dose was ¼ gr., twice; as pentobarbitol sodium 48 times, maximum dose 9 gr., average 6 gr.; and as miscellaneous sedatives 4 times, the heaviest being alurate 10 gr., so that narcosis cannot be responsible for the high fetal death rates.

3. *Delivery.*—Both infants were delivered spontaneously 51 times, the first 67 times and the second only 13 times, making 182 spontaneous births out of 558 deliveries (31.1 per cent), and by contrast cesarean section was performed 12 times (4.3 per cent). Forceps assistance was utilized 85 times for the first child and 12 times for the second; version, 6 times for the first and 125 times for the second; and breech extraction 54 times for the first and 70 times for the second, this high frequency (68.9 per cent) of interference accounting for a low average time-interval between births of 13.1 minutes, including a maximum wait in one case of eight and one-half hours.

Hemorrhage during birth was not fatal but severe in 12 (4.3 per cent) women, once due to placenta previa, 3 times due to abruptio placentae between infants, and 8 times before delivery of the placenta. The very nature of twin births and both of our groups of statistics indicate frequent hemorrhage from low placental implantation or premature separation, yet several recent case reports in the literature[17-19] would suggest rarity of such bleeding. Prolapse of the umbilical cord between births occurred 4 times, whereas one cord was so short as to require high forceps for delivery.

4. *Puerperium.*—Post-partum hemorrhage was serious in 15 cases (5 per cent), for whom 21 transfusions were essential and for as many more might well have been

TABLE I. INCIDENCE OF TWIN BIRTHS IN THE FOUR MOST COMMON CAUSES OF MATERNAL DEATH IN THE CITY OF PHILADELPHIA

CAUSE OF DEATH		NUMBER AND RATIO OF TWIN BIRTHS
Sepsis	255	5 (1:51)
Toxemia and eclampsia	156	6 (1:26)
Hemorrhage:		
A. All types	129	6 (1:21.5)
B. Post-partum	(74)	(4) (1:18)
Heart disease	49	1 (1:49)
Other causes	246	9 (1:27.3)
(Excluding abortions and ectopic gestations)		
Totals	835	27 (1:31)

used, making a total incidence of hemorrhage in pregnancy, labor, delivery, and puerperium of 36 or 13 per cent. The nonfatal and fatal morbidities are listed in Tables II and III and are much higher than for single pregnancy.

5. *Infants.*—The average weights of each pair of babies were 5 pounds 6 ounces for the larger and 4 pounds 9¾ ounces for the smaller, the largest pair weighing 8 pounds 11½ ounces and 8 pounds 1¾ ounces. One hundred eleven were breast fed, 156 weaned completely, and 176 had both breast and bottle, which had no relation to the 39 stillbirths, little relation to the 22 neonatal complications (Table IV) but may or may not have had relation to the 76 total neonatal deaths involving 40 pairs, plus 14 of the larger and 21 of the smaller of pairs according to Table V.

TABLE II. CAUSES OF NONFATAL PUERPERAL COMPLICATIONS IN 279 TWIN BIRTHS OVER TWENTY WEEKS' GESTATION. HIGH INCIDENCE OF ENDOMETRITIS ATTRIBUTABLE TO FREQUENT INTERFERENCE (68.9 PER CENT)

Sapremia	19
Deciduitis	2
Endometritis	22
Parametritis	2
Pyelocystitis	5
Pneumonia	3
Breast engorgement	2
Postoperative	3
Perineal	2
Upper respiratory infection	1
Septic splenitis	1
Total	62 (22.3%)

TABLE III. CAUSES OF DEATH FROM 279 TWIN BIRTHS OVER TWENTY WEEKS' GESTATION

1. Septicemia, peritonitis	
2. Post-partum hemorrhage. (Bilateral hydronephrosis, ascites, pleural effusion)	
3. Hemolytic streptococcic septicemia	
4. Acute dilatation of heart	
5. Abscess of broad ligament, bilateral cellulitis, acute splenic tumor, bilateral pleurisy	
Total	5 (1.88 per cent)

TABLE IV. NONFATAL COMPLICATIONS AMONG 443 SURVIVAL TWINS LISTED BY THE PEDIATRIC SERVICE

Syphilis	3
Club foot	1
Fractured humerus	1
Rickets	2
Convulsions	1
Anemia	3
Pneumonia	1
Pulmonary atelectasis	3
Facial growth	1
Pylorospasm	1
Abscess of anus	1
Congenital heart disease and undescended testicle	1
Hypospadias	1
Microcephaly	1
Hemorrhagic disease	1
Total	22 (5%)

From 165 sets of twins in the Philadelphia Lying-in Hospital, Tyson[20] found nearly 3 times as many twins born in August as in other months of the year, therefore since bi-ovular twins are three times as frequent as uniovular, and since most December twin conceptions would deliver in August rather than September, the question of possible seasonal double ovulation should be considered. From the same source, Tyson[2] also found that multiple pregnancy was the third commonest cause of 469 premature infants (Table VI).

It is noteworthy that among all of the infants, there was but one autositic monstrosity (alimentary atresia) and no instance of omphalositic, parasitic or symmetrical joined twin, and none of combined healthy, macerated and/or papyraceous twins or triplets as reported by Edmunds,[21] Collins.[23] This is of interest inasmuch as in the event of intrauterine death of one uniovular fetus as by hemiplacental necrosis or any other cause, the second should also succumb. With respect to placental anomalies, variable and frequently inadequate descriptions made it impossible to list accurately such rare possibilities as monoamnion,[24] etc.

TABLE V. CAUSES OF 76 NEONATAL DEATHS FROM 558 TWINS OVER TWENTY WEEKS' GESTATION, SHOWING THAT PREMATURITY ACCOUNTS FOR 50 PER CENT

Prematurity		44
Trauma		2
Hemorrhagic disease		2
Erythroblastosis		2
Syphilis		2
Asphyxia		1
Prolapsed cord		1
Cardiac deficiency		2
Atresia of esophagus and anus		1
Pneumonia		1
Doubtful		18
Total		76 (13.62%)
Deductible		
Prematurity	39	
Under 28 weeks		
Under 1500 gm.		
Defects	3	
Corrected neonatal deaths		34 (6.1%)

TABLE VI. PROBABLE CAUSES OF PREMATURITY AMONG 469 BIRTHS IN THE LYING-IN HOSPITAL (TYSON)

	NUMBER OF CASES	PER CENT	DIED	LIVED
Syphilis	88	18.0	60	28
Toxemia	60	12.0	41	19
Multiple pregnancy	50	10.0	24	26
Premature separation	24	5.0	21	3
Injury to mother	10	2.0	9	1
Placenta previa	9	1.9	7	2
Cardiac	9	1.9	6	3
Polyhydramnios	4	0.8	3	1
Pneumonia	3	0.6	1	2
Nephritis	3	0.6	3	0
Myoma	3	0.6	3	0
Abortion	3	0.6	3	0
Tuberculosis	1	0.2	0	1
Pyelitis	2	0.4	2	0
Acute cold	1	0.2	0	1
Asthma	1	0.2	0	1
Unknown	196	41.8	70	126

Having become "twin-conscious," the author personally observed over 2,000 practically consecutive recent pregnancies in the Preston Retreat for the special purpose of twin management, but even by particular attention to all gravida v and over, and to those who had delivered previous fraternal twins, was able to diagnose manually one set of triplets and only 19 out of 26 pairs of twins before birth, not including one positive false diagnosis in a case of polyhydramnios. When diagnosed, these twin pregnancies were supplied with extra milk and beef, vitamins A, B, D, and G and ferrous sulfate capsules and 8 out of the 14 that were diagnosed in pregnancy were admitted to the ward as "waiting women" at thirty-six weeks. To this simple plan we ascribe a slightly increased average gestation to over thirty-six weeks, avoidance of cesarean section, and protection of the mother by particular care to prevent post-partum hemorrhage as by not too heavy sedation and avoidance of ether. This was, however, offset by bleeding from one lateral placenta previa, one abruptio placentae and one instance of intrapartum hemorrhage due to an acardiacus acephalus attached almost directly to the placenta, causing abruptio placentae. There were five instances of mild and one of severe late gestational toxemia, and no deaths.

In this small series under special attention, 2 out of the 55 infants were stillborn (including the acardiacus, plus one that died from placental necrosis due to toxemia) and five died after birth, one of which was delivered at twenty-six weeks and two at twenty-seven weeks, yielding a corrected total infant mortality of 3 out of 55 infants (5.4 per cent).

SUMMARY AND CONCLUSIONS

1. Maternal, fetal, and neonatal deaths associated with twin and triplet pregnancy have been analyzed from 223,394 total births over sixteen weeks' gestation in Philadelphia from 1931 to 1937 inclusive; and detailed maternal and infant progress from 5 sets of triplets and 305 pairs of twins from the Lying-in, University and Preston Retreat Hospitals has been analyzed.

2. Maternal, stillbirth, and neonatal death rates from twin pregnancies have been shown to be increased roughly about three times over those for single births.

3. The author suggests abdominal tension resulting in renal ischemia or ureteral obstruction as a common factor in both nulliparous "low reserve kidney" and "mild pre-eclampsia" in multiple pregnancy.

4. Quantitative serum and twenty-four-hour urinary excretion of estrogen and prolan should determine whether "low reserve kidney" and many cases of multiple pregnancy toxemia are similar, and distinct from pre-eclampsia.

5. By becoming twin conscious, three-fourths of all multiple pregnancies may be diagnosed manually, and 90 per cent of suspected cases should be diagnosed by x-ray in time to provide dietetic, tonic, and physical support; avoidance of unnecessary cesarean section, and ex-

cess sedation and ether in labor; and hospitalization including preparation for immediate transfusion in all cases, thereby reducing both maternal and fetal accidents by at least one-half.

6. More time up to one hour, and fewer versions are indicated for the second birth, to allow opportunity for the uterus to readjust itself, thereby minimizing the risk of infection and post-partum hemorrhage.

7. Scrupulous management of the third stage of labor, and uterine packing for eight hours in all cases of hemorrhage before or after delivery will prevent many deaths from twin births.

8. Prematurity is the greatest infant hazard, prejudicing the neonatal period more than the natal.

9. Meticulous care, including microscopic examination, in examining the secundines from multiple pregnancy should be obligatory.

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DISCUSSION

DR. BAYARD CARTER, Durham, N. C.—The figures for North Carolina concerning twin pregnancies bear out several features of Dr. Hirst's paper. We find that approximately 40 per cent terminate prematurely. The incidence of toxemia gives roughly a figure of 45 per cent as contrasted with the incidence of about 26 per cent in the ordinary country type of patient who comes to the clinic. The incidence of abruptio placentae and the bleeding syndromes has also been greater than in the single pregnancies.

The answer to the question for the rural population in America depends upon some agency which will take the responsibility of getting these patients into a hospital early. We have asked all social agencies in the state in all cases of patients suspected of an abnormal pregnancy to give us the privilege of seeing these patients early. In that way we were able last year to diagnose for the first time a quintuplet pregnancy by means of x-ray and to avoid fatal delay. This patient was brought to the hospital in very poor condition, with a sudden acute hydramnios and an abruptio placentae.

DR. THADDEUS L. MONTGOMERY, PHILADELPHIA, PA.—It is of considerable importance to differentiate between the pathology associated with uniovular twins and that encountered in binovular pregnancy. There are certain forms of disturbance which are inseparably associated with the one or the other form of multiple pregnancy; for instance, it is possible for one of binovular twins to die in utero without influencing the vitality of the other twin, while it is impossible for one of uniovular twins to be dead for any length of time without causing the death of the other twin. Therefore, in binovular pregnancy one may encounter in one placenta aggressive conditions of the chorionic epithelium, such as hydatidiform mole, or extreme regression of the placenta and necrosis, without either lesion being present in the other placenta. On the other hand, in uniovular pregnancy fetal deformity and monstrosity is very common.

Therefore, in a careful study of the morbidity and mortality of twins it would seem wise to distinguish carefully between the uniovular and the binovular types and classify the pathologic changes under those two headings.

DR. ERWIN O. STRASSMANN, HOUSTON, TEXAS.—There are three established ways of making a diagnosis of multiple pregnancy: first, by observing the fetal heartbeats; second, by physical examination; third, by taking x-ray pictures. Accidentally, we found a fourth way of making a diagnosis of twins when we were taking fetal electrocardiograms during pregnancy.

Up to now, we did not have any objective graphic method of determining whether the fetus is actually alive. Fetal electrocardiography gives graphic evidence of the viability of the fetus in utero. We obtain at the same time in the tracings, taken from the mother, the maternal heart waves and the fetal heart waves which are easily diagnosed on account of their different rhythm, size and direction, the latter corresponding to the position of the fetus.

While taking the tests in the electrocardiographic laboratory, for I did not examine the patients otherwise, a case was sent which I did not know to be twin pregnancy. In the tracings we found two types of fetal waves in addition to the maternal deflections, one being upside down, as we see in vertex presentations, the other upwards, as we see in breech presentations. We were, therefore, in the position to tell on account of the electrocardiogram that there were twins present, that both twins were alive, that one was in a vertex, the other in a breech position. These findings were verified by x-ray picture later.

DR. HIRST (closing).—We should look with suspicion upon every large abdomen in pregnancy, x-ray and possibly electrocardiograph every one, and we should warn small maternity departments to be prepared for any emergency, especially hemorrhage, in these twin cases. In the larger institutions we should have a member of the major staff present at every twin birth if only to restrain the resident obstetrician from doing internal podalic version of the second baby until indicated.

PREVENTION AND TREATMENT OF POSTOPERATIVE THROMBOPHLEBITIS*

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(From the Mayo Clinic)

NOTWITHSTANDING a large amount of clinical and experimental study, the etiology and pathogenesis of postoperative thrombophlebitis remains obscure. As long ago as 1898, Welch stated that in any type of thrombosis there were three possible etiologic factors: a local lesion of the intima of the blood vessel, increased coagulability of the blood and relative stasis of the blood stream. It is quite possible that the comparative infrequency of postoperative thrombophlebitis is an indication that all three of the above-mentioned etiologic factors must be present in combination before the lesion develops and, if we were able to eliminate either the local vein lesion or the changes in the blood or the stasis of the blood stream, it should be possible to prevent the formation of the thrombus. From the clinical standpoint thrombophlebitis which occurs as a postoperative complication is an acute vascular accident. It follows a rather definite clinical course with a variable amount of involution and a variable amount of permanent residue. Treatment of this condition, once it has occurred, is not entirely satisfactory and the desirable attack is to prevent it from occurring at all.

Any routine program for the prevention of postoperative thrombophlebitis must take into consideration the fact that this complication is actually rather rare. For example, at The Mayo Clinic during a thirteen-year period, it occurred after only 0.7 per cent of all operations, after 1.6 per cent of all laparotomies and after 2.7 per cent of pelvic operations where laparotomy was performed. Thus, any plan of preventive treatment which is expensive, difficult, or unpleasant for the patient is hardly justified inasmuch as it would have to be carried out on such a large number of patients unnecessarily. Furthermore, the evaluation of any routine procedure can be made only after its use in several thousand consecutive cases. A satisfactory program for prevention has not yet been devised.

LESIONS OF THE INTIMA OF THE VEINS

There is statistical evidence to show that thrombophlebitis occurs more commonly after operations involving the lower part of the abdomen or the pelvic organs, in which there is of necessity some damage to the branches of the internal iliac vein. It also occurs more commonly in patients who have varicose veins of the legs. The incidence is very high after operations in patients who have had a spontaneous attack

*Read at the Fifty-First Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, White Sulphur Springs, W. Va., September 22 to 24, 1938.

of thrombophlebitis less than six months before operation. It has been presumed, although never proved, that in severe infections, lesions of the vascular intima may be produced by bacteria or toxins. Thrombophlebitis may occur as a complication of severe infections, such as pneumonia or peritonitis in patients on whom no operation has been performed, and there is an increased incidence of thrombophlebitis in patients whose postoperative convalescence is complicated by such severe infections. The prospect of attack on these various factors in order to prevent the lesion of the intima of the vein is rather poor. It goes without saying that careful surgical technique and a minimum of trauma to tissues during an operation, particularly in the pelvis, should result in a minimum of vein injury. It is also a safe rule to allow six months to elapse before performing an operation on a patient who has had an acute attack of thrombophlebitis of any type except, of course, in surgical emergencies.

STASIS OF THE BLOOD STREAM

Recently Smith and Allen have shown that the venous circulation rate may become definitely slower after major surgical operations. Various attempts have been made to modify this by having patients elevate their limbs and exercise them during the postoperative convalescence. Walters expressed the opinion that the use of thyroid extract reduces the incidence of postoperative thrombosis and embolism. Smith and Allen have shown that it does increase the speed of venous blood flow in these patients. The chief difficulty with the administration of thyroid extract has been to individualize the dosage so that each patient receives enough to produce a physiologic effect and not enough to produce unpleasant or toxic symptoms. The occurrence of relative stasis of the venous blood stream after operation is an argument in favor of keeping patients in bed for the shortest possible period of time during their convalescence. It must also be borne in mind that local venous stasis as well as injury of the veins of the legs may occur when patients are in the lithotomy or Trendelenburg position, when tight binders are placed around the hips and when hard pillows are placed behind the knees during the first few days after operation.

CHANGES IN THE BLOOD

Prevention of postoperative thrombosis by procedures designed to decrease the coagulability of the blood probably offers the best method of attack in the prevention of postoperative thrombophlebitis but work along these lines has just recently been begun. Bancroft and his co-workers have stated that they are able by means of tests of the coagulation factors of the blood to predict which patients have a tendency to thrombosis. Recently Murray and his co-workers have used heparin to prevent postoperative thrombosis. This method is apparently effective but is still rather difficult and not satisfactory as a routine procedure. There seems to be a definitely increased incidence of postoperative thrombosis in patients suffering from blood dyscrasias, particularly polycythemia and anemias of various types. It is recommended that

such conditions be brought under control before operation. In the postoperative period transfusions should be given with care and with careful attention to proper blood grouping. If a patient already has developed a thrombosis, thus indicating a thrombotic tendency, transfusions even with carefully matched blood may be followed by a recurrence of the thrombosis.

OTHER PREDISPOSING FACTORS

Statistical evidence indicates that postoperative venous thrombosis occurs most frequently in the obese (Snell) and in patients suffering from heart disease (Belt) or carcinoma (Welch), so that when operation is considered on such patients, the risk of thrombosis is relatively high. Where time permits, it may be possible to reduce the weight of the obese patient and to treat the heart disease before operation.

TREATMENT

The treatment of postoperative thrombophlebitis after the lesion has occurred must take into consideration the possibility of pulmonary embolism, management during the acute stage of the disease and the prevention of chronic venous insufficiency of the limb. Postoperative thrombophlebitis may occur in many different veins but from the practical clinical standpoint we can restrict this discussion to thrombophlebitis occurring in the lower extremities, since it is rarely found in other locations. Thrombophlebitis occurring in superficial varices is rarely of serious consequence unless it progresses and extends to the larger veins. Thrombophlebitis occurring in the short saphenous vein is fairly common and frequently passes unrecognized. Any pain occurring in the calf of the leg during the postoperative convalescence should indicate a careful examination to exclude the possibility of short saphenous thrombophlebitis. Short saphenous thrombophlebitis is chiefly important because the thrombus is likely to extend to the femoral vein at any time and in doing so the thrombus may be detached and form an embolism. Thrombophlebitis of the long saphenous vein is much less common unless there is a varicosity of this vein. Embolism is rare and subsequent venous insufficiency does not usually occur. Thrombophlebitis of the femoral and iliac veins, the so-called milk leg or phlegmasia alba dolens, usually offers no difficulty in diagnosis and there are certain definite principles which should be observed in its management. Once such a condition becomes manifest, there is a great fear in the minds of most surgeons regarding the likelihood of pulmonary embolism. However, there is clinical and pathologic evidence to show that a thrombus only becomes an embolus soon after it forms. Therefore, the danger of embolism in a patient with thrombophlebitis is on the first day of the formation of the thrombus and usually before the thrombophlebitis can be recognized clinically, or from sudden extension of thrombosis into a larger vein, or from a new episode of thrombosis in another vein.

In a series of 116 consecutive cases of fatal postoperative pulmonary embolism the clinical findings of femoral or iliac thrombophlebitis were present before death in only five cases. In one of these the thrombo-

phlebitis was first evident only a few hours before the embolism occurred. In the other four cases death from embolism occurred on the third, fifth, twenty-first, and twenty-fourth days, respectively, after the clinical onset of a femoral or iliac thrombophlebitis. In each instance necropsy revealed that the thrombus in the affected leg was intact to the level of the bifurcation of the vena cava and the remains of a fresh thrombus were found in the iliac vein of the opposite leg, thus proving that the embolism was the result of a fresh thrombosis. In the majority of cases of postoperative thrombophlebitis, there is only one episode, but there are some cases in which there are frequent episodes affecting different veins at different times. The risk of fatal embolism in a patient who has developed acute femoral or iliac thrombophlebitis of the leg, therefore, is small and usually is dependent on the occurrence of a new episode of thrombosis in a different vein. Thus the prevention of embolism in a patient with the clinical manifestations of acute femoral or iliac thrombophlebitis is a matter of preventing a new thrombus from forming and is not dependent on the treatment directed toward the thrombosis and thrombophlebitis which has already taken place.

Treatment of thrombophlebitis in the acute stage should be directed toward measures to aid the return circulation, as far as possible, and toward measures which will hasten the normal involution of the thrombus and periphlebitis. Adequate elevation will accomplish the former. Adequate external heat will aid the latter.

The liability of patients to develop chronic venous insufficiency of the leg after femoral and iliac thrombophlebitis has not been sufficiently stressed, and prevention of this chronic venous insufficiency is a very important part of treatment. Once the acute stage is over and the patient first assumes the upright position, the factor of orthostatism in retarding the return venous blood flow from the leg and increasing the pressure in the veins of the leg is added to the factor of partial permanent obstruction in the main venous trunk. Although the venous circulation may be entirely adequate for the patient in the horizontal position or in this position with the leg elevated, it is not adequate when he is standing. As the patient resumes normal activity the increased pressure in the veins may produce secondary varices and chronic static edema of the lower leg. More serious complications of chronic venous insufficiency, such as ulceration of the skin, localized indurated cellulitis, and eczema may follow. These complications are probably, to a certain extent, dependent on the inherent ability of the patient's veins to stand strain, and this varies in different individuals. Chronic venous insufficiency is more likely to develop in the obese than in the thin person, and it is also more likely to develop after extensive thrombophlebitis in a leg where venous damage, such as primary varicose veins, already existed. Once a state of chronic venous insufficiency has developed, the treatment of the limb becomes much more difficult. Prevention of such a condition may save the patient long periods of discomfort and disability.

The plan of treatment of postoperative femoral and iliac thrombophlebitis used at the Mayo Clinic is comparatively simple. As soon as

the diagnosis is made the affected leg is elevated to an angle of 30 degrees from the horizontal on a slanting frame or back rest covered with pillows. It is important that the elevation be adequate and that pressure be evenly distributed on the leg. The knee is kept in complete or almost complete extension and the hip in slightly outward rotation. The patient is allowed to move the leg occasionally in changing position. Continuous hot moist packs are applied from the foot to above the groin. The skin is first covered with a thin layer of petrolatum, then with a single layer of gauze. Around this are placed several layers of hot wet blanket material, then two or three hot water bottles and around the entire pack a rubber sheet. Packs are changed often enough to keep them hot but care is taken not to have them hot enough to burn the skin. Opiates may be necessary to control pain during the first twenty-four hours but are rarely needed after this period. The elevation and hot packs are continued until the patient's temperature has been normal for at least three days, until tenderness in the region of the veins—particularly in Scarpa's triangle and the popliteal space—has disappeared and until swelling and edema are gone from the leg below the knee. Slight enlargement of the thigh is disregarded. The hot packs are then discontinued, the leg is lowered to 15 degrees elevation for one or two days and the patient is then allowed up with a proper leg support if his postoperative condition is otherwise satisfactory. In the great majority of cases this is between ten and sixteen days after the onset of the thrombophlebitis. There are two reasons for not prolonging the stay in bed. First, the danger of embolism is past except for the small chance of a new thrombosis and, since postoperative rest in bed with resultant venous stasis is considered one of the factors responsible for postoperative venous thrombosis, prolonged rest in bed after the acute phase of the thrombophlebitis theoretically favors rather than prevents the possibility of a fresh thrombosis and embolism. Second, a long period of rest in bed favors the development of a postphlebitic neurosis (Allen and Brown), it calls attention to a disability of the limb, and it favors muscular weakness and osteoporosis in a limb with impaired circulation. In our experience it is not necessary as a preventive of chronic venous insufficiency if a proper support is worn. It is very important not to discuss the question of thrombosis and embolism with the patient. The fear of embolism and sudden death may become a real phobia and has been the cause of a number of neuroses following thrombophlebitis.

Patients with thrombophlebitis confined to the long or short saphenous veins or to varices may not need leg supports after getting up or may require only a light bandage for a short period. However, it is very important to equip the patient who has passed through the acute stage of a postoperative femoral or iliac thrombophlebitis with an adequate elastic support for his leg and to see that it is properly applied before he gets out of bed for the first time. The support should prevent any swelling of the lower leg and foot after standing or walking. Elastic cloth bandages are uniformly inadequate, rubber and cloth mesh bandages are usually inadequate and most elastic stockings unless very heavy

and carefully made to measure are inadequate. The most satisfactory support is a pure solid rubber bandage 3 inches by 15 feet. It can be removed and reapplied at any time if the tension is not right. It is heavy enough to prevent any postphlebitic edema if properly applied and its wearing qualities are excellent. Its disadvantages are that it may produce discomfort from heat, particularly in the summer, that the patient must learn to apply it, that some patients, chiefly women, object to its appearance and that some skins are sensitive to rubber. Second choice in supports is a heavy elastic stocking made carefully from measurements.

The support should be applied from toes to knee with only a small portion of the heel exposed and this should be covered by the heel of the shoe. In using the rubber bandage a long white cotton stocking is put on the leg first. It is difficult or impossible to apply a support, either bandage or elastic stocking, to the knee and thigh that will not slip and will not irritate the popliteal region when the patient walks. Some swelling of the thigh may occur when the patient is active but usually this disappears spontaneously in time and serious complications of venous insufficiency rarely occur in the thigh. The patient should be instructed in the application of the bandage. It should be wrapped snugly but not under tension. It should be applied in the morning before he gets out of bed, removed and rewrapped at noon and at about 6 P.M., and removed again at bedtime. For one or two months the patient should sleep with his leg on a pillow. With the bandage on, ordinary activity is permitted except that standing without walking should be minimized. When sitting, the feet should be elevated on a stool if possible. Exercises with the leg elevated are advisable. After three months the bandage is left off for a half day and, if no swelling of the leg appears, for longer periods. If the swelling is minimal, a lighter bandage may be worn for a longer period of time. If it is definite, the heavy bandage should be continued for one or two more months and another trial made without it.

The results of treatment according to the plan mentioned above, in 54 carefully studied cases of acute postoperative femoral and iliac thrombophlebitis were as follows: Pain became minimal within twenty-four hours after treatment started and was completely relieved within five days from the onset of phlebitis in 66 per cent of the cases and within ten days in 91 per cent of the cases. Fever in cases uncomplicated by other infections disappeared within one week from the onset of phlebitis in 81 per cent of the cases and within twelve days in all cases. Swelling of the leg below the knee and edema had disappeared within fourteen days from the onset in 81 per cent of the cases and within eighteen days in all cases. Tenderness in Scarpa's triangle and the popliteal space was gone within sixteen days in all cases. Eighty-one per cent of the patients were allowed up from the tenth to the sixteenth day after the onset, depending on disappearance of symptoms, and all were up within twenty-four days. In over half of the patients the pain disappeared in two to four days, the fever in five to seven days, the swelling in ten to fourteen days, the tenderness in ten to fourteen

days, and they were up in ten to fifteen days from the time of onset. It has not been shown that leeches, roentgen therapy, diuretics or injections of sodium thiosulfate added to simple, but adequate, heat and elevation have shortened the acute stage or hastened the involution of postoperative femoral and iliac thrombophlebitis.

Of our 54 patients, only one died of pulmonary embolism. This occurred twenty-eight days after the onset of a left iliac thrombophlebitis. At necropsy the thrombus in the left iliac vein was found to be intact and well organized, and the remains of a fresh thrombus (unrecognized clinically) were found in the right iliac vein. This patient had been kept in bed an unusually long time, twenty-four days after the onset of the left iliac thrombophlebitis, because of other postoperative complications but had been up for four days when death occurred. Three patients of the 54 died subsequently of the disease for which operation had been performed (carcinoma). The remaining 50 have been followed by subsequent examination or letter for from three to eight years following their thrombophlebitis. Not all were treated with the same type of leg supports. The ultimate results from the standpoint of chronic venous insufficiency are as follows:

Thirty-five patients were equipped with the heavy rubber leg bandages. Twenty-seven of these (77 per cent) were able to discard the bandage within two to twelve months after the onset of the thrombophlebitis and subsequently did not develop edema, varicose veins, ulcers, eczema, or pain on walking. Three patients developed mild to moderate static edema of the leg after discarding the bandage but no other signs of venous insufficiency. Two patients subsequently developed chronic edema and definite varicose veins with some pain in the leg after discontinuing the bandage. (One of these stopped wearing the bandage after six weeks, against advice.) Three patients had to continue to wear the bandage and are still doing so, as going without it produces rather marked pain and swelling of the leg. These represent severe degrees of chronic obstruction of the iliac vein. None of this group has developed ulcers, cellulitis or stasis eczema. Of 3 patients who were equipped with elastic stockings instead of rubber bandages one was finally able to discard the stocking without further trouble. Two developed chronic edema in spite of the support. Of 12 patients given cloth elastic bandages, 4 ultimately discarded them without further trouble. Five developed chronic edema. Two developed edema, pain and varices and subsequently were given rubber bandages which they are still wearing and one patient developed severe pain, eczema, and a chronic ulcer of the leg.

For comparison a study was made of 50 patients who were seen at the Mayo Clinic during the same five-year period and who had had a postoperative femoral or iliac thrombophlebitis less than five years previously. This group of patients had had various types of treatment. Many of them had been kept in bed for periods of several months after the acute stage of the thrombophlebitis but none of them had worn heavy rubber bandages or adequate supports. Some had had no sup-

ports at all. Only 5 patients in this group (10 per cent) had no trouble with the affected leg, 11 (22 per cent) had mild swelling and pain after walking, 15 (30 per cent) had rather marked edema and had developed definite secondary varicose veins, and 19 (38 per cent) developed not only edema, pain, and varicose veins, but also ulcers and cellulitis. Six patients out of the 50 in this group had developed a definite postphlebitic neurosis and 5 of these had been kept in bed for more than two months after the acute stage of the phlebitis.

From a more detailed comparison of this group of patients with those who were given adequate support, we feel that the prevention of chronic venous insufficiency following postoperative femoral and iliac thrombophlebitis with its more serious sequelae of ulceration and cellulitis depends, not on the length of time that the patient is kept in bed following the acute stage, but on the adequacy of the supporting bandage which he wears after resumption of orthostatic activity.

SUMMARY

No satisfactory routine procedure has been devised for the prevention of postoperative thrombophlebitis. Certain measures have been discussed which will help to minimize the three essential factors of local vein injury, slowing of venous blood flow and alteration in the coagulability of the blood.

Postoperative thrombophlebitis may be successfully treated in the acute stage by adequate elevation of the limb and the use of extensive hot wet packs locally. It is advisable to get the patient up as soon as the temperature has been normal for three days, swelling below the knee has subsided and local tenderness in the involved veins has disappeared. As soon as the patient is out of bed it is necessary to equip him with an adequate leg support and for this a heavy pure rubber bandage is recommended. The bandage can usually be discarded in from three to twelve months without the subsequent appearance of any signs or symptoms of chronic venous insufficiency. Once the clinical picture of acute postoperative femoral or iliac thrombophlebitis has appeared, the danger of fatal pulmonary embolism is small.

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DISCUSSION

DR. FREDERICK H. FALLS, CHICAGO, ILL.—Trauma and infection, particularly the latter, are in my opinion the most important factors in the production of thrombophlebitis. For this reason in doing hysterectomies we endeavor to limit as much as possible the crushing of tissues which are to be left in the pelvis after operation. All total hysterectomies are drained vaginally to reduce the danger of infection of clots present in vessels severed at operation.

In my experience there has quite frequently been evidence of thrombophlebitis before the loosening of pulmonary embolus. Furthermore, we are continually on the look-out for evidence of small emboli which produce pleuritic pain, possibly some cough and expectoration but none of the dramatic symptoms seen in large pulmonary emboli. These small emboli may precede the larger ones by several days, and when noted should indicate the maximum immobilization of the patient until sufficient time has elapsed for the thrombus to become well organized, which may, in our opinion, be about three weeks. We do not allow the patients to sit up in bed, turn over, or use the bed pan without assistance. I believe they would be safer still if strapped on a Bradford frame and we have done this occasionally. We have noticed frequently in cases of thrombophlebitis that a rise in pulse rate out of proportion to the rise in temperature frequently precedes the clinical signs of the condition.

We do not share Dr. Counseller's fear of creating a neurosis by telling the patient with thrombophlebitis of the possible dangers of pulmonary embolism. We feel that to get the cooperation which is so essential in the management of this condition it is necessary to tell most patients exactly what the consequence of failure to cooperate on their part may be.

The following statistics show that in a period of ten years we have had 21 cases of thrombophlebitis among 2,785 operations, an incidence of 0.67 per cent. These were all pelvic laparotomies. There were 3 deaths, a mortality of 0.107 per cent.

DR. WILLIAM T. BLACK, MEMPHIS, TENN.—At the John Gaston Hospital, Memphis, in a series of 4,205 cases in the Gynecological Service 7 cases of thrombophlebitis were reported. There were 3 deaths due to an embolus. One of these was a cardiac embolus, the other two pulmonary.

No doubt cases of thrombophlebitis of mild degree occur following pelvic operations, which are never diagnosed as such. Mild unexplained pelvic infections with a slight rise in temperature, pain, and tenderness are often due to thrombophlebitis.

Thrombophlebitis is more likely to occur in a dehydrated, anemic and septic patient. Therefore, fluids and blood transfusions are indicated preoperatively and postoperatively. Keeping the patient in one position too long during and after an operation predisposes to a thrombus formation. Those with a previous history of thrombophlebitis should be handled with great care during an operation for fear of an embolus. Gentleness in technique is good prophylactic treatment.

If the tests could be carried out routinely as recommended by Bancroft and his co-workers, no doubt thrombophlebitis could often be prevented. I have used thyroid extract, as advised by Walters, but have been unable to form definite conclusions. Sodium thiosulphate may be used. Heparin promises more than any other agent as demonstrated by the splendid work of Murray and Best. The newer preparation of heparin is said to be free of any toxic property and is of course a splendid anticoagulant.

DR. W. WAYNE BABCOCK, PHILADELPHIA, PA.—We have all seen the pale swollen leg that not a few patients carry throughout the remainder of their lives. While the involvement of superficial veins alone may later give rise to varicosities and ulcer, the condition is less serious and may be taken care of by sclerosing injections. It is involvement of both the superficial and deep veins that is particularly harmful.

I wish to emphasize the danger of traumatizing thrombosed veins during the acute stage. I recall a physician who died within a few minutes after his leg was massaged for severe pain associated with the onset of a thrombophlebitis.

At times the thrombus becomes infected and an abscess forms. As ligation of a proximal vein was advised for thrombosis of the lateral sinus, thirty years ago I ligated the long saphenous for a severe phlebitis of the leg to prevent an extension of the process. A fatal shower of emboli followed. A similar procedure done by a colleague was also fatal. On the other hand, I do not recall a fatality where the surgeon had waited for the abscess to point and had merely incised. We now believe that ligation or removal of the thrombus early in any case of septic thrombophlebitis is very dangerous.

DR. ALBERT MATHIEU, PORTLAND, OREGON.—If an abdominal binder is tight enough to do any good, it is harmful; and if it is not tight, it is worthless. I am very much opposed to the binder that binds the patient like a plaster of Paris cast, because some of these cases of thrombophlebitis have originated in veins in the abdominal wall. I highly disapprove of pillows under the patient's knees and hospital beds which buckle up under the patient's knees. By these means the patient's circulation in the legs is impaired. The patient rather should be encouraged to move the legs frequently. I have seen one death following vaginal hysterectomy with the site of the thrombus in the veins beneath the gastrocnemius muscle.

DR. F. S. WETHERELL, SYRACUSE, N. Y.—We have for some years followed a method which seems to have cut down what previously was an incidence of thrombophlebitis similar to that reported by Dr. Counseller. The method is simple and undoubtedly many of you use it, and consists simply in the inhalation of CO_2-oxygen every two hours for three minutes. It is impossible to breathe deeply and rapidly for a greater length of time. I continue that regime for two or three days, or longer, if the patient seems to be a potential candidate for thrombophlebitis. It is used routinely in every case, whether pelvic or abdominal.

I think the members of this Association have here a problem which they might well work out together.

DR. WILLIAM A. COVENTRY, DULUTH, MINN.—In my own town there are two surgeons who in order to prevent thrombophlebitis write out so many orders that the patient is exhausted if the orders are properly carried out. I, myself, have for the last five years simply had the patients move about in bed on their own power. This exercise promotes circulation in the deep veins.

PROFESSOR CHARLES BURGER, BUDAPEST, HUNGARY.—I wish to call your attention to a therapy that in the very beginning, or if the lesion has not progressed too far, may influence the course favorably and lessen the pain; that is x-ray therapy. The application of leeches in the inguinal region may, according to our experience, be favorable in diminishing the pain, and one can make use of this when x-ray is not available.

DR. V. S. COUNSELLER (closing).—I am impressed with the fact that embolism and phlebitis occur more frequently in spring than in the fall. This observation has been made previously at the University of Illinois. In June and July of this year we have had more rain and have seen more phlebitis than in the same months for many years in Minnesota.

The late Dr. George Brown instituted at our clinic a method of management of postoperative thrombophlebitis and of embolism. As soon as such a condition is encountered the Vascular Service is notified. Extreme care has been taken to teach assistants how to care for such diseases and a conference with the patient is held before he leaves the hospital in order to instruct him as to further treatment. A follow-up system has also been instituted.

RECENT DEVELOPMENTS IN DIAGNOSIS AND TREATMENT OF HYDATIDIFORM MOLE AND CHORIOEPITHELIOMA*

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WHEN the literature of the last few years is reviewed and contrasted with former writings, it is evident that there has been intelligent activity and noteworthy advances as regards hydatidiform mole and chorioepithelioma. Up to 1930 the diagnosis of hydatidiform mole rested on the demonstration of hydatid vesicles, and the diagnosis of chorioepithelioma was rarely made until metastases had occurred. Since 1929, when Zondek discovered that gonadotropic hormone was present in the urine of patients with hydatidiform mole, and was greatly increased in amount over that of normal pregnancy, and since 1930, when this same discovery was made with relation to chorioepithelioma, diagnosis, treatment, and prognosis of these diseases have changed to a remarkable extent. An analysis of the extensive papers written prior to 1930, including about 1500 cases of chorioepithelioma and probably ten times as many moles, shows that the mortality rate of mole was approximately 12 per cent and that of chorioepithelioma 60 per cent. A review of the world's literature for the last three years, involving 576 cases of mole and 266 of chorioepithelioma, shows the mortality rate now to be approximately 2 per cent and 10 per cent, respectively.

At present it seems that diagnostic criteria are adequate but that diagnostic acumen is lacking, and that maximum results in treatment are not being obtained because of inertia on the part of the clinician or nonacceptance of the newer criteria. Because of insufficient experience no man can speak authoritatively on these diseases, but a review of contemporary literature enables us to assemble the important factors responsible for improved diagnosis and reduced mortality.

The most important single development in diagnosis and treatment is the test for chorionic gonadotropic hormone. It is generally accepted that this test is positive and that the amount of hormone is increased in mole and chorioepithelioma.

Recently there have been reports of positive pregnancy tests with the contents of lutein cysts, with fluid aspirated from the chest, with fluid from hydroceles, and with various tissues of the body. When one considers that patients harboring mole or chorioepithelioma have great quantities of chorionic gonadotropic hormone in the blood, it is obvious that this hormone will be present in all fluids and tissues of the body.

While the cerebrospinal fluid gives a negative test in normal pregnancy, it gives a positive test in mole and chorioepithelioma. Smith

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and Smith found that when chorionic cells become neoplastic they do not contain estrin in amounts comparable with those found in normal placentas. May not this lack of estrin in pathologic chorionic cells be the factor accounting for the excessive amount of gonadotropic hormone!

Although all authorities agree on the value of the biologic pregnancy test in the diagnosis of mole and chorioepithelioma, it should be noted that there have been many misconceptions of the test—laboratory errors (2 per cent), too much reliance on a single test, and clinical and pathologic judgment at variance with the test. The pregnancy test is always positive only if there is living chorionic tissue present or when the stored hormone has not been completely absorbed.

The qualitative test is not sufficient since the increasing amount of hormone associated with these diseases is detectable only by a quantitative assay. Nevertheless, one should not overlook the fact that at about the sixtieth day of normal pregnancy there is an enormous amount of the hormone. In the pursuit of mole and chorioepithelioma by means of biologic pregnancy tests, one must be certain that normal pregnancy is not present.

Quantitative estimations of the hormone by some other method than that of Aschheim and Zondek have been attempted. Schoeneck determined the minimal amounts of urine, at various stages of normal pregnancy, required to produce positive Friedman reactions. In the Brindeau-Hinglais method curves showing the hormone content of the serum were developed by injecting measured quantities of the patient's blood serum into rabbits.

Quantitative tests are at times impractical, inexpedient, or even impossible. When only qualitative tests are used, one must be aware of the following facts: (1) the test is positive in the presence of living chorionic tissue, which includes normal pregnancy; (2) the test is also positive in hydatidiform mole, chorioepithelioma, or metastases of either disease; (3) the test may be negative in missed molar abortion; (4) the test may be positive for six weeks following the passage of a mole because of stored hormone in the body; (5) if a test is positive two months after the passage of a mole, and normal pregnancy has been excluded, it is likely that living molar tissue is still present or chorioepithelioma has developed; (6) in the presence of lutein cysts after all living chorionic tissue has been removed, the test will be positive until these cysts regress because the hormone is stored in them; (7) a positive test one month after the removal of a chorioepithelioma is strong evidence of metastasis; (8) the spinal fluid gives a negative test in normal pregnancy and a positive test in mole or chorioepithelioma; (9) absolute reliance should not be placed on one test, and in questionable cases the test should be checked and rechecked; (10) the test should be used in all questionable conditions where the element of chorioepithelioma might exist; and (11) the biologic test should overrule contrary clinical and pathologic findings. During a period of a week or so following mole, there might exist a

nidus of chorioepithelioma which is too small to produce a sufficient quantity of hormone to be detectable by methods now extant. Although such a nidus is a rarity, it probably explains those few cases reported in which there was a negative test at some period during the transition of mole into chorioepithelioma. If such a nidus exists, it will not be long before it grows sufficiently to give a positive test, or, the test will be positive before the disease gets beyond easy clinical control.

Little progress seems to have been made toward the solving of the etiologic puzzle involved in these conditions, nor do we know all we should concerning their interrelated pathology. There just begins to creep into the literature reference to the fact that interested pathologists are making apparently successful attempts to differentiate between the benign mole and the mole with malignant potentialities. Hertig's report on a series of paraffin blocks, slides, and follow-up records of over 100 cases of mole is a challenge to pathologists to organize their material and study it meticulously, not only with the idea of attempting to establish malignant potentialities in moles, but also to detect the early or small focus of chorioepithelioma. If this is to be accomplished, it can be done only by correlated study of a mass of material.

When the diagnosis of mole is uncertain the patient should be treated conservatively, but once the diagnosis is certain, it is probably best to empty the uterus at once through the vagina. An important part of the treatment of mole is watchfulness for the advent or presence of chorioepithelioma. Evidence indicates that there are many cases of simultaneous occurrence of these two diseases. In the follow-up treatment there should be repeated biologic pregnancy tests which, when correlated with the clinical findings, will show the presence or absence of chorioepithelioma. The greatest pitfalls in the follow-up treatment of mole are lack of knowledge that chorioepithelioma may ensue and the misconception of the biologic pregnancy test.

Early diagnosis and immediate hysterectomy offer the best chance of cure of chorioepithelioma. Total hysterectomy or subtotal hysterectomy should depend on whether or not the cervix is involved or otherwise diseased. It is generally conceded that in most cases the removal of the primary growth results in retrogression of metastases. Extensive metastases need not delay the operation.

The presence of lutein cysts in conjunction with these diseases is a very interesting biologic phenomenon. These cysts appear to be sequential rather than the cause of mole or chorioepithelioma, and since they are apparently the result of constant bombardment of increased chorionic gonadotropic hormone, the longer the mole or chorioepithelioma exists the larger the cysts will become. Fewer lutein cysts will be reported in the future, for we have every reason to believe that ultimately diagnosis will be made before they are formed. In my cases of chorioepithelioma following mole, in which

diagnosis was made early and hysterectomy done, there were no lutein cysts visible in any of the ovaries. Torsion is the only indication for removal of lutein cysts because they regress when the primary focus is removed. The ovaries should not be removed unless they are definitely involved by the disease. Only a few surgeons have had the courage of their convictions and the pioneering spirit to remove the uterus and leave the ovaries in young women. These few have been paid for their courage and with no loss to the women.

Reports of treatment by roentgen ray and radium are beginning to appear. Some authors feel that irradiation is of value when the patient has an inoperable growth or when the surgical risk is great. Others think that irradiation should be used in addition to operation, either before or after, and that when it is employed, the dose should be as large as the patient can tolerate. It is contended that chorioepithelioma and mole are extremely radiosensitive because of their embryologic cell type. While treatment by irradiation seems to be well founded theoretically, and while a few cures have been reported, the majority of the reports are not very promising.

There is a strong feeling against curettage in the diagnosis of chorioepithelioma as it is liable to disseminate the lesion or cause perforation of the uterus, and because it may be extremely misleading and result in mismanagement of the case where the lesion is buried deep in the myometrium and inaccessible to the curette. A great deal of this argument can be applied to hysterotomy as treatment of this lesion. Naïve dependence on curettage or hysterotomy may result in tragic sequelae.

Since hysterectomy is the operation that cures, it seems best that we abandon curettage and not take up hysterotomy. While abandonment of curettage might seem extremely radical, when we estimate the rare good it does, the harm it does, and what better information we can get through biologic pregnancy tests, it seems advisable. Just as in acute appendicitis and ectopic pregnancy, all patients should be operated upon as soon as the diagnosis is made in order to obtain the best results and serve the common good. In a few cases it appears that the uterus was removed needlessly, but these cases are rarities and need not influence our conduct. While occasionally there is injected an argument by a pathologist that certain chorioepitheliomas might have regressed and hysterectomy have been avoided, the report of regression, which is a rarity, should not dominate the situation. Waiting for regression of the chorioepitheliomatous lesion surely does not constitute one of the factors responsible for the lowered mortality rate obtained at the present time. A study of the recent literature almost invariably shows that the patient was cured when the disease was diagnosed early and hysterectomy performed immediately, and that the deaths were recorded among the group in which diagnosis and treatment were delayed or in which the disease was of long standing. In 1928 Ewing said he had "been unable to find any record

of operative cure of choriocarcinoma." Recently cures of such cases have been reported, and two of my patients who had choriocarcinoma were cured.

There is a suggestion that some lytic substance might possibly be evolved as a cure. This is based on the fact that approximately 80 per cent of pregnant women have living chorionic cells in their circulation, and that after delivery a lytic substance is present in their blood which destroys the chorionic tissue, that is, serum of normal women during pregnancy is able to destroy migratory chorionic cells, while serum from women with chorioepithelioma does not seem to possess this lytic action. The lack of this substance is held to be responsible for the almost 100 per cent mortality in teratomatous chorioepithelioma of the ovary and the testicle. It has been recommended that selected patients with hopeless choriepithelioma be treated by intravenous administration of large doses of serum from the pregnant human female, and if the reaction is favorable that serum from one of the lower animals, such as the mare, be investigated.

Notwithstanding the fact that recent advances have done much toward the perfection of diagnosis and treatment, there remains much to be done. Careless and fragmentary reporting of cases must be avoided because more harm than good is done by slipshod reporting of paradoxical cases replete with inconclusive evidence. Editors should refuse papers on such a controversial subject unless these papers show all the earmarks of thorough, scientific study and honesty of purpose. Furthermore, loose concepts must be abolished; more exact knowledge and better interpretation of the tests for gonadotropic hormone must be had; and a technic better than is at present extant is needed so that the most minute amount of living chorionic tissue can be revealed. And it is to be hoped that ultimately criteria will be formulated that will establish potential malignancy of mole, thereby enabling us to prophesy the advent or to determine the existence of chorioepithelioma. Whether this will be done by the pathologic investigator or by the endocrinologic investigator remains to be seen. A wide exchange of material under the guidance of an unified group of competent pathologists might be the solution. The highest percentage of cures will be gotten when there is judicious correlation of clinical history, verified histologic examinations, and intelligent interpretations of the biologic pregnancy tests. It would appear if modern criteria are used, early diagnosis made, and early operative treatment instituted that the woman with chorioepithelioma will have approximately a 95 per cent chance to get well and keep her ovaries.

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DISCUSSION

DR. T. L. MONTGOMERY, Philadelphia, Pa.—Some few years ago, after making a study of our cases at the Jefferson, I presented a paper before the College of Physicians of Philadelphia on the subject "Aggressive Phases of the Chorionic Epithelium." Upon re-reading the observations of that paper, I find no reason to change the opinions expressed therein and desire to present them to you.

1. A study of the life cycle of the chorionic epithelium reveals in the course of pregnancy normal periods of aggression and regression.

2. Abnormal stimulus at fertilization may manifest itself either in the form of early regression with ultimate necrosis of the placenta and intrauterine death of the fetus, or in aggression eventuating in hydatidiform mole or chorioepithelioma.

3. The presence in one side of a binovular pregnancy of premature regression, or of aggression and hydatidiform mole, while the neighboring embryo is normal, indicates that these phenomena arise upon fertilization of the ovum and are inherently hereditary in nature.

4. The aggressiveness of the trophoblastic elements varies widely in intensity from the mild forms of hydatidiform mole to the extremely malignant types of chorioepithelioma. It appears unnecessary and impossible to "pigeonhole" each pathologic specimen in the diagnostic classifications such as have been suggested by Ewing and others.

5. Through the production of lytic substances nature has provided in normal pregnancy for the limitation of chorionic growth to the wall of the uterus and the destruction ultimately of those bits of syncytium that wander through the mother's circulation.

6. Even in hydatidiform mole and chorioepithelioma of pregnancy, some attempt is made in this same direction by these obscure or "x" factors of maternal resistance, and if the main mass of tissue is removed mechanically, oftentimes the outlying deposits will be taken care of by these lytic processes.

In the light of such observations it would appear that we have two factors which must be given attention in our treatment of the aggressive phases of the chorionic growth: (1) the innate growth stimulus which occurs at fertilization; and (2) a maternal resistance factor (x) which develops during the course of the growth.

The presence of a large amount of gonadotropic-like hormone is evidence of ascendancy in growth of the chorionic epithelium. In normal pregnancy this epithelial formation which is at first aggressive, later undergoes regression and is ultimately cast off as the placenta and membrane, upon which the maternal factors of lysis quickly assume the ascendancy and destroy the syncytial strands which remain at the placental site.

In hydatidiform mole and chorioepithelioma natural regression does not take place, and if the system is not rid of the nefarious and parasitic material, the host will be destroyed. How the host will take care of the outlying strands of tissue and the migrant cells after removal of the primary mass becomes the important consideration in formulating a prognosis. Ultimately we will find a way to increase lytic substance in the maternal system and perhaps raise it to a level which will be effective in chorioepithelioma.

DR. S. A. COSGROVE, JERSEY CITY, N. J.—It is very evident that the single factor responsible for the change from the almost hopeless picture of a few decades ago to the decidedly good prognostic outlook of the present is the application and evaluation of the repeated quantitative estimation of gonadotropic hormone. Therefore it seems to me that we should not tolerate a condition which he describes in the statement that quantitative tests of this sort are at times "impractical, inexpedient or even impossible." In a matter of so great moment the profession should be able to devise means whereby such quantitative tests might be made available to sufferers from these diseases.

The situation could be briefly summed up, except for a small percentage of laboratory errors, in the following way:

1. When, consistent with clinical history, a supposed pregnancy shows by repeated quantitative hormonal tests a much higher titer of hormone values than is normal in pregnancy, hydatidiform mole or chorioepithelioma may be diagnosed with high probability.

2. When, following the extrusion of a hydatidiform mole, persistent or reappearing hormonal tests in exceedingly high titer show a progressive increase, then chorioepithelioma should be unhesitatingly diagnosed and operative interference promptly instituted.

I would be inclined to amend only one statement made by Dr. Mathieu in his discussion of the significance of these tests. He says, "The biologic test should overrule contrary clinical and pathological findings." I would prefer the statement: "The repeated *positive* biologic test should overrule contrary clinical and pathological findings." But if negative biologic tests are not consistent with suggestive clinical findings, then the result of biologic tests should not lull one into a false sense of security, as has been so significantly shown by a case reported by Schumann.

Too great emphasis cannot be placed on Dr. Mathieu's insistence on three most important principles:

1. The prompt operative treatment of mole and persistent biologic follow-up after its extrusion.

2. Prompt hysterectomy in every case where the existence of chorioepithelioma is even highly probable. I believe total hysterectomy better in all these cases, lest occasional involvement of the cervix be overlooked.

3. The conservation of the ovaries in those cases where chorioepithelioma is diagnosed early, and the ovaries are not definitely diseased.

DR. F. J. SCHOENECK, SYRACUSE, N. Y.—Dr. Mathieu mentioned a quantitative Friedman test in connection with the diagnosis of hydatidiform mole. We have developed a comparatively simple procedure which may be carried out in any laboratory that is doing Friedman tests.

We have established the minimal amounts of urine that will give positive reactions during the early weeks of pregnancy. In general, positive reactions may be obtained between the sixth and twelfth weeks of pregnancy with amounts varying from 1 c.c. to 0.1 c.c. As a rule the smallest amounts are necessary between the eighth and eleventh weeks.

With such normals established, we can easily determine specimens in which there are greater amounts of hormone present. This is done by injecting the test animals with 0.025 c.c., 0.0125 c.c., etc., of urine. In actively growing moles we have obtained positive reactions with as little as 0.0063 c.c. The only requisite is additional test animals. Inasmuch as we laparotomize the rabbits and use them again and again, the expense of the test is not too great.

There are several cautions that must be observed in the use of such a quantitative test. Aside from hydatidiform mole, we have found at least two other conditions in which more hormone is excreted than in the instance of normal pregnancy, notably excessive vomiting of pregnancy and multiple pregnancy. Thus, we can imagine a case of multiple gestation associated with excessive vomiting and threatened abortion, giving not only a perfect clinical picture of hydatidiform mole, but being confirmed by laboratory findings. Such a case erroneously diagnosed as mole and treated as such by cleaning out the uterus might be, to say the least, embarrassing.

Also, there are certain types of hydatidiform mole that in our experience have not been associated with an excessive excretion of hormone. We had two instances in which there was actually less hormone than would be expected for normal pregnancy. Neither of these moles on expulsion showed the typical pathologic picture. According to our interpretation, they were undoubtedly undergoing degeneration, presenting a solid mass with only very few vesicles.

A final point: While it is necessary to employ the quantitative test to differentiate hydatidiform mole from normal pregnancy, when we are dealing with a possible chorioepithelioma, the ordinary qualitative test is quite sufficient. While the quantitative test is interesting scientifically and may be of importance from a prognostic viewpoint, the ordinary test will suffice for diagnosis.

DR. LOUIS E. PHANEUF, BOSTON, MASS.—I have had a personal experience with 9 hydatidiform moles and 4 chorioepitheliomas. These cases were published in the *New England Journal of Medicine*, 217: 270, 1938. Dr. Arthur T. Hertig, pathologist at the Boston Lying-In Hospital, listed in the discussion of these cases certain observations which are helpful in settling the question of malignancy. He regarded certain moles as benign because of the following general histologic picture: 1. Normal chorionic epithelium. 2. Slight, undoubted benign hyperplasia without mitoses or anaplasia. 3. Moderate to marked benign hyperplasia with occasional anaplastic cells, that is, those of increased size with enlarged, irregular hyper-

chromatic and darkly staining nuclei. Hertig based the diagnosis of "potentially malignant," "probably malignant," or "malignant" on one or more of the following features: 1. Invasion of villous stroma by relatively undifferentiated chorioepithelial elements. 2. Moderate to marked anaplasia of the epithelium, either with or without mitotic activity. 3. Tissue culture-like growth of detached chorioepithelial elements, usually in fairly large masses and growing upon the surface of a blood clot.

I prefer panhysterectomy with double salpingo-oophorectomy in chorioepithelioma because in the presence of this highly malignant new growth, the chances of cure are enhanced by removing the entire pelvic organs. Dr. Mathieu is not in accord with this since he is of the opinion that the lutein cysts will regress when the primary focus, the uterus, is removed.

DR. HENRY SCHMITZ, CHICAGO, ILL.—About eight years ago I reported to this Association observations on eight cases. Out of seven primary choriocarcinomas, two were treated with radium and roentgen rays. Both survived the five-year period, one for ten years, when she succumbed to a heart disease; the other one was treated twenty-one years ago and is still living today. Three patients had a panhysterectomy with postoperative roentgen irradiation. One patient had only a hysterectomy. The absolute cure in the seven primary cases was 85.7 per cent. The mortality in one case resulted from late diagnosis and infection. The recurrent choriocarcinomas did not react to any kind of treatment.

The good end results of treatment depend on early diagnosis. The Aschheim-Zondek test has enabled us to render an early diagnosis. Recently we had a case of hydatidiform mole in which the Aschheim-Zondek test was obtained with 1/250th of a cubic centimeter of urine. The patient was curetted and a twin pregnancy was found. The chorioepithelioma was entirely confined to one of the pregnancies.

DR. EMIL NOVAK, BALTIMORE, MD.—It should be emphasized that we cannot make a final diagnosis with these biologic methods. The final diagnosis in chorioepithelioma must be on the basis of a pathology. Many of the biologic characteristics which Dr. Mathieu has described apply equally to benign hydatidiform mole and malignant chorioepithelioma.

I am impelled to emphasize this point because of Dr. Mathieu's statement that he thinks that with the employment of these biologic methods a patient with chorioepithelioma will have a 95 per cent better chance of cure than formerly. That is a rather startling statement. First, chorioepithelioma is a very malignant tumor, in the great majority of cases. Second, it is a very rare tumor. In our laboratory at the Johns Hopkins Hospital we have specimens of about 48,000 cases and among them we have not had more than about 8 or 9 chorioepitheliomas. Some years ago Dr. Symmers of New York reported that in some 32,000 autopsies he had never seen a chorioepithelioma. We should be inclined to lean backward in reaching such a diagnosis.

Sometimes pathologic diagnosis is quite simple, in other cases difficult. In a borderline case it is difficult to say whether we are dealing with a benign hydatidiform mole, with marked trophoblastic proliferation or with a real chorioepithelioma. When we get large masses of trophoblast growing in bulk, with few or no villi, and destroying the uterine muscle, and with abundant evidence of anaplastic activity, there is little difficulty about the diagnosis. But in a perfectly benign hydatidiform mole if the sections are from the uterine wall, where the mole is getting plenty of blood supply, and not from the vesicles in the uterine cavity, we may be confused by the large masses of trophoblastic tissue, which nevertheless is not evidence of malignancy. I believe that many more mistakes of diagnosis are made in this particular field than in any other. Even normal pregnancy has often been mistaken for chorioepithelioma because of the frequent presence of numerous trophoblastic cells deep in the musculature beneath the implantation area, though this is entirely normal.

In view of what we know as to the malignant course of genuine chorioepithelioma, and its frequently very early metastases, it seems almost incredible to me to expect a

reduction of mortality to only 5 per cent as Dr. Mathieu has suggested, no matter how conscientiously and intelligently one may apply the biologic methods which he has discussed.

DR. JOE V. MEIGS, BOSTON, MASS.—Lutein cysts, in my experience, should not be left behind if they are large. We have had two such cases in recent years. In one the cysts were the size of oranges and were bleeding. The patient was in severe shock. The other had a cyst the size of a child's head on each side. I doubt the regression of any of these cysts.

One fact has not been stressed today, which I think is probably true, that following a normal pregnancy one is more likely to have a choriocarcinoma and after hydatidiform mole a chorioadenoma that is less malignant.

It is essential to remove the cervix in chorioepithelioma. One of our patients developed a tumor five years after operation. There is a chain of lymphatics running down into the cervix from the body of the uterus.

Placental polyps are confusing because months or even a year after delivery a piece of placenta left behind can cause bleeding and microscopic differentiation is often very difficult. It should be recognized that there may be placenta left in utero for a long time.

DR. JAMES K. QUIGLEY, ROCHESTER, N. Y.—I wish to relate very briefly two interesting phenomena that I saw in March in connection with a hydatid mole. The first was an extreme degree of what we would ordinarily call a toxemia, with hypertension, albuminuria and extreme jaundice so that the patient almost died from the toxic state before she expelled the mole. Second, she developed a lutein ovarian cyst the size of a child's head. After the expulsion of the mole there was a diminishing quantitative Friedman test, but the cyst kept increasing in size. I removed this cyst but left 2 or 3 small lutein cysts of the opposite side.

DR. MATHIEU (closing).—Regarding Dr. Schoeneck's discussion, we must remember that Evans in a very careful study determined that there was a very high degree of hormone content about the sixtieth day of normal pregnancy. This high point must be considered when we make a quantitative estimation of the hormone in the diagnosis of hydatidiform mole or chorioepithelioma. However, it is the increasing amount of hormone which is important.

As to Dr. Novak's comment, he is perfectly right. I did put the percentage of possible cures rather high. My study of the literature revealed the fact that the mortality rate is now only about 10 per cent for women with chorioepithelioma. I merely want to prophesy that with increased interest in the subject, and more definite knowledge regarding the disease, this mortality surely could be cut to 5 per cent. Dr. Novak feels that I have stressed too much the importance of the Aschheim-Zondek reaction and have not paid sufficient attention to the pathologic side in regard to diagnosis. Many of the errors in diagnosis and mismanagement of cases, as seen from a study of the literature, seem, however, to have been due to the inability of the pathologist to arrive at a definite, correct conclusion.

MANAGEMENT OF BREECH DELIVERY IN PRIMIPARAS*

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(From the Department of Obstetrics, Harvard Medical School, and the Boston Lying-in Hospital)

MOST articles written on the subject of breech delivery present figures concerning fetal and neonatal mortality. This approach is somewhat suggestive of the statement that while people talk a lot about the weather no one really does anything about it. Hence the decision, from a study of fetal and neonatal mortality in one institution over a period of fifty years, to formulate what we believe to be the best method of management of breech delivery in the primipara. It may be added parenthetically that such conclusions as are drawn may be applied with equal force to breech delivery in the multipara, as our experience with both groups has been strikingly parallel.

Table I presents an outline of 2,035 miscellaneous breech deliveries and 58 cesarean sections occurring on the house service of the Boston Lying-in Hospital during the years 1888 to 1937 inclusive. The cases selected from this material are limited to 500 pelvic deliveries and 32 cesarean sections performed upon healthy, primiparous women at full term, whose babies at birth weighed six pounds or more. In accordance with an article previously published[2] we have eliminated from consideration 453 breech deliveries and 6 cesarean sections complicated by factors such as pre-eclampsia, eclampsia, chronic nephritis, syphilis, diabetes, cardiac disease, hydramnios, placenta previa, ablatio placentae, and prolapse of the cord, all of which in themselves add to the gravity of prognosis for the baby. We have eliminated "non-viable" infants, macerated at birth or grossly malformed. We have eliminated premature infants weighing less than 5 pounds at birth, and immature babies weighing from 5 to 6 pounds. Finally, since the subject lies outside the scope of this survey, we have eliminated mature multiparous deliveries.

In computing mortality, stillbirths and neonatal deaths are classified as *mechanical* or *intercurrent*. Deaths from mechanical causes occur from asphyxia or trauma, demonstrable either clinically or by postmortem examination. Deaths from intercurrent causes are due to such factors as congenital heart disease and incidental pathology of early neonatal life.

Table I summarizes the results in the 500 breech deliveries and 32 cesarean sections. The figures, which yield a mortality of 10.2 per cent for all pelvic deliveries and of 3.1 per cent for cesarean sections, do not indicate a rosy prognosis for the infant.

It is at this point that our crude statistics should be analyzed, in order to determine whether in fifty years there has been any trend

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toward improvement in our results, and to discuss any possible improvement which may have occurred. The figures of the 500 breech deliveries, recast in another form, will illustrate the point.

During the years previous to 1921 the general management of breech delivery consisted in the classically conservative attitude expressed by the formula, "Leave the case to nature. Guide the trunk until the umbilicus is born. Be ready to assist delivery at any time should delay occur." The first primiparous breech delivery entrusted to me in my intern days in 1920 was conducted in this way. The breech slowly came over the perineum. The fetal heart was suddenly lost. The baby was extracted, stillborn, the placenta, prematurely separated during the second stage, following immediately. On March 1, 1921, Irving and myself undertook a special assignment on breech delivery for one year, conducting such cases both in the Hospital and Out-Patient Department under an activist policy which was expressed briefly as, "Extract at full dilatation." Our results, published in 1926,[4] showed a lowering of primiparous breech mortality from 11 per cent to 7.4 per cent, which we believed justified our policy. This policy has been continued since.

TABLE I. DELIVERIES OF BREECH PRESENTATIONS AT THE BOSTON LYING-IN HOSPITAL FROM 1888 THROUGH 1937

		INFANTS DELIVERED	INFANTS WELL	INFANTS STILLBORN OR DIED	MORTALITY PER CENT
A. Breech deliveries					
1. Uncomplicated	(2,035)				
a. Primiparous	(691)				
(1) Premature		102	45	57	55.8
(2) Immature		89	77	12	13.4
(3) Mature		500	449	51	10.2
b. Multiparous	(768)				
(1) Premature		119	54	65	54.6
(2) Immature		89	85	4	4.5
(3) Mature		560	514	46	8.2
2. Complicated	(453)				
3. "Nonviable" (macerated and malformed)	(123)				
B. Cesarean sections	(58)				
1. Uncomplicated	(52)				
a. Primiparous		32	31	1	3.1
b. Multiparous		20	18	2	10.0
2. Complicated	(6)				

Some further evidence in justification of routine extraction has been adduced from two other sources.

1. A series of 87 consecutive breech cases as a special assignment undertaken by me from Oct. 1, 1931, to Apr. 1, 1933. Eighty-three were delivered through the pelvis with the expectation of securing a live infant, with two neonatal deaths, a mortality of 2.3 per cent.[1]

2. The results of delivery of 351 mature primiparous single infants from 1913 to 1937 inclusive, which show a decrease in intercurrent and mechanical mortality from 9.8 per cent in the years from 1913 to 1920 inclusive, to 5 per cent from early 1928 through 1937 (Table II).

The real difference, however, in the results of the two policies, conservative and activist, did not stand forth in clear contrast until the records of breech deliveries from 1888 through 1912 were tabulated and added to those from 1913 through 1937. This is shown by Fig. 1, and by Table III in which the deliveries from 1888 to March 1, 1921, are

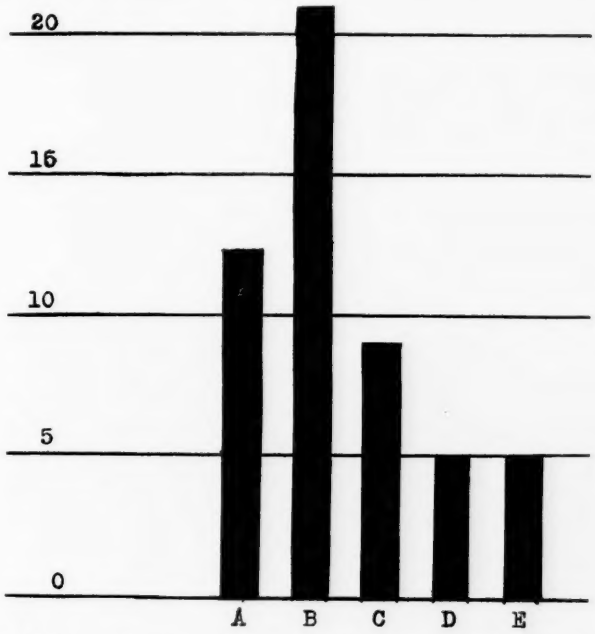

Fig. 1.—Mortality in breech delivery (1888–1937). Primiparous mature single infants. *A*, 1888-1905, 82 deliveries, 10 fatalities, 12.2 per cent; *B*, 1905-1920, 100 deliveries, 21 fatalities, 21.0 per cent; *C*, 1921-1928, 100 deliveries, 9 fatalities, 9.0 per cent; *D*, 1928–1932, 100 deliveries, 5 fatalities, 5.0 per cent; *E*, 1932–1937, 100 deliveries, 5 fatalities, 5.0 per cent.

contrasted with those from the latter date through 1937. The differences between mortality rates of 16.9 per cent and 6.3 per cent for single deliveries and 16.3 per cent and 6.2 per cent for single and multiple are worthy of remark.

It will not be maintained, at this point, that the crude ratio of 16.3 to 6.2 represents, in our experience, the comparative risks to the infant by delivery and extraction. Certain factors in connection with the mechanical deaths in the two periods should be studied first. Table IV summarizes these fatalities, using a classification which has been suggested before.

Group A.—Mechanically easy delivery of apparently normal infants, with neonatal death occurring a few hours to several days later with evidences of intracranial hemorrhage. This group may be likened to those deaths following normal vertex delivery with similar results.

TABLE II. MORTALITY IN BREECH DELIVERY. PRIMIPAROUS MATURE SINGLE INFANTS 1913-1937

	INFANTS DELIVERED	INFANTS WELL	INFANTS STILLBORN OR DIED	FATALITIES		MORTALITY PER CENT
				INTERCURRENT	MECHANICAL	
1913 -1920	51	46	5	0	5	9.8
1921 -1928(p)	100	91	9	2	7	9.0
1928(p)-1932(p)	100	95	5	1	4	5.0
1932(p)-1937	100	95	5	0	5	5.0

TABLE III. MORTALITY IN BREECH DELIVERY, MATURE INFANTS, BEFORE AND AFTER MARCH 1, 1921

	IN-FANTS DE-LIVERED	IN-FANTS WELL	INFANTS STILL-BORN OR DIED	FATALITIES		MORTAL-ITY PER CENT
				INTER-CUR-RENT	MECHAN-ICAL	
Primiparous, single						
1888—Mar. 1, 1921	183	152	31	1	30	16.9
Mar. 1, 1921—1937	299	280	19	3	16	6.3
	482	432	50	4	46	10.4
Primiparous, single and multiple						
1888—Mar. 1, 1921	196	164	32	1	31	16.3
Mar. 1, 1921—1937	304	285	19	3	16	6.2
	500	449	51	4	47	10.2
Multiparous, single						
1888—Mar. 1, 1921	204	178	26	10	16	12.7
Mar. 1, 1921—1937	300	284	16	4	12	5.3
	504	462	42	14	28	8.3
Multiparous, single and multiple						
1888—Mar. 1, 1921	231	202	29	11	18	12.5
Mar. 1, 1921—1937	329	312	17	4	13	5.1
	560	514	46	15	31	8.2

TABLE IV. MECHANICAL MORTALITY IN BREECH DELIVERY

	GROUP A	GROUP B	GROUP C	TOTAL
1888—Mar. 1, 1921				
Deaths following normal or assisted delivery	1	4	1	6
Deaths following extraction after full dilatation	2	2	7	11
Deaths following extraction before full dilatation	1	0	2	3
Deaths following extraction after manual dilatation	0	0	11	11
	4	6	21	31
Mar. 1, 1921—1937				
Deaths following normal or assisted delivery	0	0	0	0
Deaths following extraction after full dilatation	2	3	4	9
Deaths following extraction before full dilatation	0	1	3	4
Deaths following extraction after manual dilatation	0	1	2	3
	2	5	9	16

Group B.—Mechanically easy delivery, with stillbirth, or birth of a child in manifestly poor condition who cannot be revived or who dies shortly afterwards.

Group C.—Mechanically difficult or traumatic delivery.

The cases in Group A are those in which, prima facie, good results are obtained, the fatal termination being unpredicted at the time of birth. Undoubtedly some factor inherent in the breech mechanism is involved, as shown by Eardley Holland[3] and others, and it is unlikely that any amount of watchfulness or skill in delivery can ever do away completely with this type of result.

The cases in Group B deserve some detailed consideration. It should be stressed again that in this group delivery is easy, but is followed by stillbirth or by birth of a child dying shortly thereafter. The 11 cases are summarized.

1888. No. 4091. Breech on perineum two hours. Fetal heart rose to 170. Baby extracted. Gasped few times. Died.

1889. No. 4422. Normal breech labor. Baby stillborn. All efforts to resuscitate child failed.

1894. No. 6865. Normal breech labor. Fetal heart 172 at entrance at 5 P.M. No further record on this point. Fully dilated at 10 P.M. Baby born at 10:40 P.M. Stillborn.

1897. No. 8586. Assisted breech delivery. Child somewhat asphyxiated. Revived in hot water. Cry feeble. Did not nurse well. Failed. Died third day. "Cause probably difficult labor."

1906. No. 14629. Spontaneous delivery to umbilicus. No trouble with arms or head. Baby gasped. Heart stopped a half hour later.

1910. No. 17201. Extraction after half hour in second stage without progress. One arm extended. Head easily delivered. Baby gasped once or twice. Died in twenty minutes.

1925. No. 32933. Bagged for premature rupture of membranes without onset of labor. Considerable bleeding after bag was expelled. Fetal heart O.K. at first, later began to fall. Easy extraction. Baby stillborn.

1926. No. 35159. Easy extraction at full dilatation. Baby stillborn. No evidence of prolapse of cord or separation of placenta.

1926. No. 36198. Admitted after forty-three hours of labor outside. Fetal heart 180 on admission. Cervix 3 to 4 fingers dilated. Early contraction ring, easily dilated. Extraction without difficulty, with fetal heart O.K. at beginning. Baby stillborn.

1928. No. 39654. Prolapsed foot with os 4 to 5 fingers dilated. No progress in thirty minutes. Traction made on foot. Second leg brought down. Fetal heart lost. Easy delivery from this time on. Baby stillborn.

1931. No. 5506. Easy breech extraction. Forceps to aftercoming head. Baby breathed with head on perineum, but not after delivery. Autopsy showed bilateral tentorial tear, with laceration of vein of Galen.

While trauma may have been of moment in the two Group B cases delivered through undilated cervices, the history of nine of them indicates that the second stage of breech labor is dangerous to the unborn child. In one at least bleeding suggested some degree of placental separation, while in eight others something happened, quite possibly an involvement of the cord. Since it has been shown that frank prolapse of the cord is five times as frequent in association with breech delivery as with the general run of hospital deliveries, this assumption seems worthy of consideration.

The cases in Group C resulted fatally because of frankly traumatic factors. The evidence from the records indicates that pelvic contraction was of moment in only 5 of the 500 deliveries, a surprisingly small proportion, indicating that the judgment of the Staff to allow delivery to proceed via the pelvic route was justified in 99 per cent of the cases. On the other hand, delivery of the infant through an incompletely dilated cervix or following accouchement forcé was strikingly frequent in the Group C fatalities in both periods surveyed, and illustrates the danger to the infant which these maneuvers entail.

The tabulation of these figures has no definite significance in indicating that extraction following full dilatation was more or less dangerous to the infant than normal or assisted delivery. Table V, taken from the records from 1888 to 1912, indicates the mortality in the normal group to be 8.9 per cent, while that in the extracted group was 10.9 per cent. On the other hand 2 of the deaths following extraction occurred in cases in which the pelvis had been misjudged, while, as would be expected, extraction was done during this era only on cases where it was deemed that unassisted delivery would be dangerous or impossible.

TABLE V. COMPARISON OF MORTALITY FOLLOWING BREECH "DELIVERY" AND BREECH "EXTRACTION," 1888-1912

	TOTAL CASES	DEATHS	GROUP A	GROUP B	GROUP C	MORT. %
Normal or "assisted" deliveries	67	6	1	4	1	8.9
Extraction following full dilatation	64	7	2	2	3	10.9

From a priori reasoning there is some ground for the belief that extraction, properly done following full dilatation, might be less dangerous to the infant than the vicissitudes of normal or assisted delivery. The mechanism of breech birth is essentially three-fold in nature, involving successive submechanisms of breech, shoulders, and head. It is stated by Le Lorier,[6] Williams,[8] Piper,[7] and others that the three submechanisms present successively larger circumferences to pass through the birth canal, similar to a truncated cone passing small end first. Von Jaschke[5] states "In footling presentations the danger to the child is increased, in that the circumference of the breech, noninclusive of the legs, is only 24 cm., hence the aftercoming head is the means whereby full dilatation of the os is encompassed." Williams[9] gives the suboccipitofrontal circumference of the head, which later passes through the os, as 34 cm. There are, of course, some differences in these figures according to the size of the infant, but they strongly suggest that full dilatation of the os in relation to the breech is often insufficient dilatation for the aftercoming head. Should full dilatation for the breech mean insufficient

dilatation for the shoulders, extended arms are sure to result. Very little experience with breech delivery, indeed, is required to appreciate the fact that extended arms are common, and that delivery of the head is often associated with a sense of resistance as the head passes the cervix.

Before concluding this phase of the subject one other factor should be considered. Prior to 1921 little if any medication was used during labor. The patient's second stage was conducted with her cooperation, good or bad though it might be. At the most, ether to the obstetric degree was given. When and if progress was delayed, it became necessary to anesthetize the patient. This was often a hurried performance and by the same token the manipulations carried out were often hurried and therefore relatively poorly done. Subsequent to 1921 the policy of breech extraction was carried out under full surgical anesthesia from the start. More time could be taken to do a slow and methodical extraction without any sense of frantic haste. More recently analgesic medication has been the order of the day. Conscious effective cooperation of the patient in the second stage, if it were desired, has been practically abolished, while at the same time the human impulse to "do something" before full dilatation has undoubtedly been kept in abeyance.

It is for the foregoing reasons that we believe that our policy since 1921 of extraction during the second stage of labor has paid dividends in a reduction of our stillbirths and neonatal fatalities. While we are not dogmatic in the original concept of extraction *immediately* at full dilatation, we believe, nevertheless, that extraction under complete anesthesia after full dilatation has been attained is safer for the infant than normal or assisted breech delivery.

Thus far the subject of cesarean section for primiparous breech delivery has been barely touched upon. If we recall the history of this operation in general, we are reminded of the fact that it is primarily undertaken in the interest of a living child which cannot pass through the pelvis of its maternal host. The diagnosis of cephalopelvic disproportion is relatively easily made in the case of the vertex presentation, and may, under proper supervision, be delayed until a test of labor has given the final answer. On the other hand, when the breech presents, the fetal head is the last and largest end of the cone destined to pass through the pelvic girdle, and the test of labor, so useful in vertex presentation, is quite out of the question.

Despite this unfavorable aspect of the situation there are still some favorable factors. The size of the baby's head can often be more accurately estimated when it lies in the fundus than in the lower abdomen: in fact the size of the entire baby can often be more clearly made out by clinical palpation; in our series all four cesarean sections done "for large baby" yielded infants weighing over 9 pounds. Finally, clinical measurements of the pelvis, both external and internal, are equally available regardless of the nature of the presentation.

We have had some hope that measurement of the head in the fundus by stereo-x-rays might help in elucidating this problem of cephalopelvic adaptability. It has unquestionably been of value in the diagnosis of hydrocephalic and anencephalic infants, the delivery of which alive, setting aside religious scruples, is to be deprecated. It is successful in giving an accurate measurement of the silhouette of the baby's cranium in 65 per cent of the cases at the first attempt. On the other hand this silhouette is that of the occipitofrontal plane in 89 per cent of the cases, of an oblique plane in 3 per cent, and of the important biparietal plane in only 8 per cent;[1] consequently *the* essential biparietal diameter must be estimated within limits from the occipitofrontal diameter before it can be compared with the patient's conjugata vera. Finally, while the stereoroentgenometric technique which we have used has not yet satisfied us that it measures the maternal pelvis accurately, we can still avail ourselves of digital measurement of the pelvis, under anesthesia if necessary.

The results of our 32 uncomplicated primiparous breech cesarean sections have been shown in Table I. The one neonatal death in the series occurred on the eleventh day post partum from intercurrent erysipelas, so that no fetal mortality from mechanical causation has occurred. All the mothers survived. The neonatal deaths occurring after two multiparous breech cesarean sections resulted, respectively, from impetigo and hydrocephalus (the latter in 1918).

Table VI reviews the 32 sections according to indication, dividing them into two groups, those before 1932 and those in 1932 and subsequently when x-ray investigation was started.

It is noticeable that in both groups the majority were for contracted pelvis, elderly primiparity, or estimated large babies. That the estimate of the weights of the large babies was accurate has already been com-

TABLE VI. INDICATIONS FOR CESAREAN SECTION IN PRIMIPAROUS BREECH DELIVERY

	NO. CASES	X-RAYS
1911 through 1931:		
Contracted pelvis	7	0
Active tuberculosis	1	0
Elderly primiparity (37, 38, 44)	3	0
Ankylosis of left hip	1	0
Estimated large baby (9 pounds 8 ounces)	1	0
	13	0
1932 through 1937:		
Cephalopelvic disproportion by clinical and x-ray measurements	7	7
Elderly primiparity (41, 42, 43)	3	1
Estimated large babies (9 pounds 5 ounces, 9 pounds 5½ ounces, 9 pounds 11 ounces)	3	3
Funnel pelvis	2	1
Flat pelvis	2	0
Longstanding rupture of membranes without labor	2	0
	19	12

mented on. Elderly primiparity certainly deserves consideration in deciding upon cesarean section for primiparous breech delivery, for an expected fetal mortality of 4 to 6 per cent may be a high price to pay for delivery through the pelvis of what is likely to be the patient's only child.

CONCLUSIONS

1. The cases discussed in this survey have been limited to normal primiparas at full term with living undeformed infants in utero all weighing 6 pounds or over. Study of the records and treatment of the 532 deliveries has been undertaken to determine the proper management for such cases in the future.

2. The management of breech delivery resolves itself primarily into an estimate of the relative advisability of abdominal section versus delivery through the pelvis.

3. Minor degrees of pelvic contraction are very important when the breech presents, since the test of labor as applied to vertex presentations is of no value for the aftercoming head.

4. The size of the infant in utero must be carefully considered. X-ray measurements have proved to be of value in helping to arrive at this estimate.

5. It is a wise policy to use the x-ray in any case in which abdominal delivery is contemplated, not only to confirm and control the size of the infant but also to detect gross skeletal abnormalities undiscovered by clinical examination.

6. The age and fertility of the mother must be considered.

7. If pelvic delivery is selected the second stage should be terminated by breech extraction under full anesthesia before the birth of the umbilicus, as classically recommended, has occurred.

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DISCUSSION

DR. ARTHUR H. BILL, Cleveland, Ohio.—In Dr. Goethals' splendid paper he has backed up by convincing statistics his claim that extraction at the time of full dilatation is preferable to assisted birth. I am in absolute agreement with this and see no reason whatsoever for allowing labor to go on in a breech case after full dilatation. This has been my policy throughout my entire practice, and I could add statistics to prove this point.

Of course, we must first of all rule out those cases in which there is a disproportion between the bony pelvis and the fetal head. Since there is no such thing as a test of labor, this should be done before labor by careful measurements and x-ray. Inasmuch as there is some error in measurements of the fetal head and pelvis, I think that where there is a reasonable doubt as to the probability of the

head passing through the pelvis a cesarean section should be done. When the baby is to be delivered through the pelvis the secret of success is in having the way clear for its passage through the entire birth canal, that is, by removing as far as possible the resistance of all the soft parts, including especially the cervix and lower uterine segment. Resistance of the cervix and lower uterine segment is probably responsible for most of the bad results in cases of breech presentation.

When delivery is performed at the time of full dilatation the patient is put under a complete anesthetic and the vaginal canal is ironed out thoroughly by manual dilatation. Usually an episiotomy is performed. The hand is then passed up through the os and full dilatation is assured. Estimation of the size of the os is made by spreading the fingers as far as possible to what would be the size of the aftercoming head and not merely the size of the breech. Then the lower uterine segment is relaxed by complete anesthesia. Relaxation by anesthesia is very important. If these precautions are taken, the arms very seldom go up over the head during extraction. In assisted birth when the breech descends to the perineum and uterine contractions are continuing, the precautions mentioned are not taken. The vaginal canal has not been ironed out and is more or less resistant. The cervix may not be dilated to the size of the aftercoming head and the lower uterine segment is not relaxed. If the arms go up over the head it is usually because they are drawn up by the resistance of the cervix and lower uterine segment. The same resistance makes delivery of the aftercoming head difficult. These few points illustrate the advantage of performing the extraction early rather than waiting and allowing the patient to do as much as she can. We must also bear in mind that the easiest time to bring down the legs is when the breech is high rather than when it is low down in the pelvis.

I would like to sum up what I think are the important steps in the management of a breech delivery. When there is full dilatation proceed to deliver the baby. Thoroughly iron out the whole vaginal canal and usually perform an episiotomy. Never take for granted that the os is dilated even though the breech has passed through it. Examine the cervix and dilate the os manually if necessary. Relax the lower uterine segment by complete anesthesia, bring down both feet, one at a time, and do the extraction. Do not use the Mauriceau grasp but deliver the aftercoming head by suprapubic pressure on the head aided by the guiding traction and flexion produced by the finger in the child's mouth. Be sure that the head does not lie in the anteroposterior diameter of the pelvic inlet. Rotate the head so that it will enter the pelvic brim in the transverse or oblique position. Forceps on the aftercoming head are, to my mind, rarely necessary. If this procedure is followed I see no reason why there should be much more difficulty in extracting a breech in the case of a primipara than in that of a multipara, or following a podalic version.

DR. WARD F. SEELEY, DETROIT, MICH.—I have reviewed the cases of breech delivery from two of our Detroit hospitals for a five-year period. One of these is a charity, teaching institution, the other a private hospital. In both the essential principle of management was essentially the same for breech delivery, that is, interference only when indicated. The fetal mortality by this more conservative treatment in our hands is practically the same as that reported by Dr. Goethals.

For a period of five years there was a total of 13,685 deliveries among which were 773 breech positions. Of these, 270 were in primiparous women. If deductions are made for cases of toxemia, placenta previa, prolapse of the cord, abruptio placentae, nonviable infants, etc., as suggested by Dr. Goethals, in order to arrive at a true rate of risk from breech position itself, we have 182 cases upon which to base our opinion. To arrive at this figure we have deducted twins and nonviable prematures, but have included all cases of eight months' duration or more and all infants weighing 5 pounds or more. In other words we have made no deduction for Dr. Goethals' classification "immature." We made this slight departure from Dr. Goethals' classification because our cases include a number of colored women, whose babies, although well developed, usually average less in weight than the white, and also because we feel that a fetus of eight months should have an excellent chance of surviving.

Among the 182 uncomplicated, mature, single primiparous breech deliveries, there were 9 fetal deaths or 4.9 per cent. There was no maternal mortality.

Six babies were stillborn and 3 died in the neonatal period. Five deaths occurred in cases with breech extraction and four after spontaneous delivery. All but one death were probably the results of birth trauma.

There were only 2 cesarean sections for pelvic contraction in the 270 cases. I can agree with Dr. Goethals that the proper evaluation of methods of delivery in these cases is difficult. And all information obtainable, both clinically and by x-ray examination, is none too much.

In conclusion, let me state that we are not opposed to breech extraction as evidenced by the fact that 42.2 per cent of our series were thus delivered, but we prefer to use it only upon indication. We also believe that the indication will arise less often if deep analgesia in the second stage is avoided.

DR. J. M. BERGLAND, BALTIMORE, MD.—We have had some recent reports from the obstetrical clinic of the University of Maryland which indicate that the operation of external version is not as difficult as we had supposed. My own experience with this procedure has been very discouraging, but I believe that, in view of this report which has not been published, we will give the matter at the Johns Hopkins more attention.

Many years ago I helped Dr. Williams do the first pubiotomy ever performed in the city of Baltimore. The operation has now been almost entirely discarded in view of new procedures such as low cervical cesarean sections, which are now very properly in vogue. However, I still think there is a place for pubiotomy. In many cases we are uncertain as to the size of the aftercoming head in spite of the most modern methods for measuring this part of the baby and quite often we underestimate the diameters of the head and have to end up with a craniotomy in order to deliver the child. I believe that when we are in grave doubt as to the question of disproportion we should place the Gigli saw in position and then if attempts to deliver the head fail, we can complete the operation of pubiotomy by cutting through the bone and the child's head can then be freed without special difficulty. If the full operation is not necessary the saw is removed and no damage is done.

DR. GEORGE W. KOSMAK, NEW YORK CITY.—Dr. Goethals did not go into the details of the technique which he employed in these cases. I would like to know whether at any time he made use of the Voorhees' bag? There is a group of breech presentations in which the bag can be used with advantage to secure that satisfactory dilatation of the cervix which is so essential. I admit that these cases must be rather carefully selected and probably in the greater number of breech cases it is unnecessary, and yet an experience with two women within two weeks convinced me of the desirability of that procedure. One was a primipara in the eighth month who had a very rigid cervix, the other a multipara with a thick cervix, at term. In both of those cases I used the Voorhees' bag, using next to the largest one in the primipara and the largest size in the multipara. I think the rupture of the membranes might have swept the cord down but the insertion of the bag improved the chances of getting a satisfactorily dilated cervix.

I hoped that Dr. Bill would mention the protection of the child with a warm towel as it is born. I think the respiratory efforts on the part of the baby are very often stimulated by the cold air of the immediate surroundings. You must remember that the temperature inside is about 98 and outside is very likely to be 65 or 70. The envelopment of that baby in a warm towel as it is being born is very important.

DR. WILLIAM T. MCCONNELL, LOUISVILLE, KY.—In breech presentation it is especially difficult to determine the relationship of the fetal head to the pelvis. While it is true that ordinarily the head will correspond in size to the size of the baby's body, and while it is true that the way the pelvis of the baby comes down into the pelvis of the mother will give you some idea as to the relative ease with which that head will pass through, yet it is often a very difficult thing to tell what the relationships are. A number of things may help us. One is the history of the size of the babies this mother has already had; another is the acumen with which we are able to palpate the size of the baby in this mother; another is the use of the x-ray, to determine to a minute degree the size of the pelvic inlet.

DR. IRVING W. POTTER, BUFFALO, N. Y.—I was very much pleased to hear Dr. Goethals use an expression which no one else has used here today, that is the "misjudged" pelvis. Now if it is true, as I believe, that breeches occur more frequently in the funnel-shaped pelvis, we are then usually dealing with more or less of a contraction. In women who are past 35 or 40, who have never had a child and will probably never have another, we lean to the operative side, that is, cesarean section.

Our technique is a little different than what has been described. As soon as the lower uterine segment is effaced and the os is dilated we bring down both feet and terminate these cases as footlings. We deliver the baby slowly and carefully by traction as far as possible. If the child does not move we do not pull it until we find where the obstruction is. Then as the scapula appears we put a finger in the posterior axillary fold and deliver both shoulders as anterior shoulders, never going up and pressing as we used to do and having a paralyzed arm. The operation of episiotomy we never do. It seems to me an operation entirely unnecessary. But we do use the Piper forceps more often as years go on.

Dr. Kosmak spoke of protecting the baby to prevent it from breathing too soon. We have watched babies in our versions make respiratory efforts and have seen no harm ever come from it. We never wrap a baby unless it is so slippery that we cannot hold it.

DR. GOETHALS (closing).—We agree with Dr. Bill's practice in regard to using forceps on the aftercoming head according to indications. We try pressure on the head from above first. If this does not work, the use of forceps is a life-saving measure without doubt.

Comparing our statistics as best we could with those of others we found that by taking the same types of cases we had about the same results. I am not entirely certain that in the long run, with many thousands of cases, the policy of routine extraction after full dilatation will necessarily be any better than the other policy *in the same man's hands.* Of course, if external version can be done it is by all odds the thing to do. If we have a 6.2 per cent mortality in primiparous breech delivery and less than 1 per cent in normal vertex delivery, the advantage of having the baby turned is perfectly obvious.

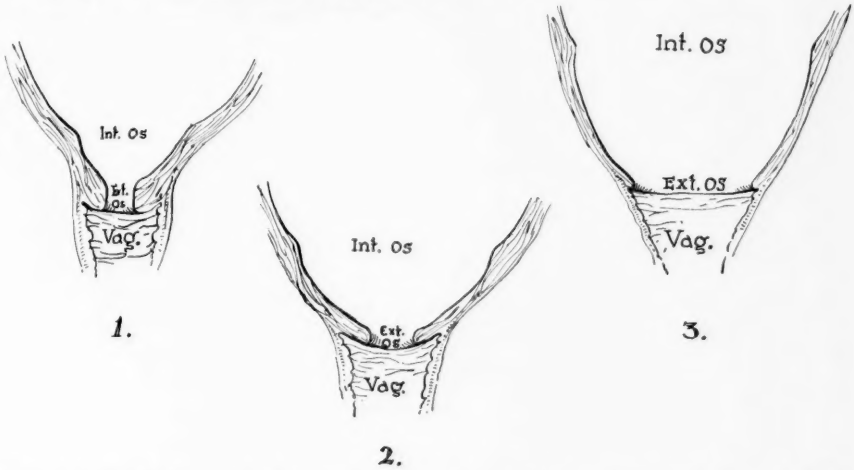
In two or three instances we did use the Voorhees' bag. The indications were particularly for premature rupture of the membranes and lack of progress of the first stage. We do not use hot cloths to wrap the baby in, because we feel that a few respiratory efforts do no harm if the accoucheur is sure he can get the baby out without asphyxia resulting.

THE PITFALLS OF PODALIC VERSION AND EXTRACTION*

MILTON G. POTTER, B.A., M.D., F.A.C.S., BUFFALO, N. Y.
(From the Millard Fillmore Hospital)

IN THE performance of internal version, I believe that it would be advantageous to recall again not only that deep anesthesia, "ironing out" of the vagina, the modified Walcher position and lack of haste are essential prerequisites, but also to emphasize some of the things the operator should not do, when attempting this type of delivery, which have not been written about before.

The purpose of this paper is not to deal with the indications for this procedure but rather to impart the results of our experiences, and always to keep in mind the following precautions.



Figs. 1 to 3.—Degrees of effacement of the lower uterine segment and dilatation of the external os.

1. *Never Attempt a Version and Extraction (Nor Any Other Type of Delivery) Until the Lower Uterine Segment Is Effaced and the External Os Completely Dilated.*—The careless or ignorant observance of this rule has done more to discourage the use of this operation than all other factors and this peculiar situation arises, I believe, from the lack of a uniform and fixed definition of complete dilatation of the os.

It has been the custom in our teaching in recent years to avoid the term dilatation of the cervix entirely, and speak only in terms of the degree of effacement of the lower uterine segment and the degree of dilatation of the external os (Figs. 1, 2, 3). Our distinct impression is that too little attention is paid to the lower uterine segment in labor and that it is the rule rather than the exception to find obstetricians failing to recognize the distinction between incomplete effacement of

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the lower uterine segment with a rigid, nonnegotiable cervix and complete lower uterine effacement with a paralyzed external os, which appears not to be completely dilated, but which disappears under deep anesthesia, when the examining fingers are spread apart and allows the entrance of the hand into the uterus.

It must be remembered that the crux of the situation is the complete effacement of the lower uterine segment and that dilatation of the external os is one of degree only.

Effacement begins before the onset of labor and when it is complete we have the beginnings of a retraction ring which is relaxed under deep anesthesia so that version can be completed.

We consider the external os dilated when the lower uterine segment is completely effaced and the external os, under deep anesthesia, admits three fingers and when spread readily admits the hand into the uterus. This is not saying we deliver the patient when the cervix is three fingers dilated, for it must be remembered that there may be a three finger dilatation of the external os without complete effacement. In other words in the first instance, we have a paralyzed external os with a possible rim present which melts away under easy pressure of the fingers, along with complete effacement of the lower uterine segment, and in the second instance, we have a three-finger dilatation without complete lower uterine effacement which means we have a nonnegotiable external os which will not admit the hand without tearing and is therefore not dilated.

Not infrequently we see arrest of the fetal head in midpelvis.

The lower uterine segment is effaced, but the head which is in the transverse or posterior position is above the external os, which is perhaps three fingers dilated and will never become more dilated because of the absence of the head as a dilator at the external os. It is a flaccid, paralyzed external os which will become swollen and edematous if delivery is not effected at once.

2. *A Version Is Best Attempted When the Head Is at the Brim and Has Had a Chance to Mold.*—The prevalent opinion that an ideal case for the use of version and extraction is a floating head is erroneous. The head should, at least, be at the brim and there should be partial molding of that fetal head with flexion, if the operator expects his extraction to be successful. If the pelvis is large and the baby small, it is possible that no difficulty will arise, because the head can be pushed into the pelvis from above, but given a slightly contracted pelvis and a normal-sized baby, with no molding of the head, the operator will expose that fetal head to injury, just as he would in the delivery of the aftercoming head of a breech case with similar pelvic and fetal measurements.

It must be remembered that a floating head, even though it can be pushed into the pelvis, is the type of case which carries a greater risk, and we can therefore expect a higher fetal mortality rate.

3. *A Version Should Never Be Attempted When the Uterus Is Dry and Firmly Contracted Around the Fetus* (Fig. 4).—Failure to heed this warning may easily result in rupturing the uterus and yet we have

seen attempts to do version under these conditions. Of course this does not exist excepting after a long labor, ruptured membranes and molding of the uterus about the fetus and, in the presence of a retraction ring, unsuccessful attempts with forceps. Then the operator, with his obstetric judgment affected perhaps by fatigue, tries a podalic version, and the result is a dead baby and often a ruptured uterus.

4. *When the Gloved Hand and Arm Are Once Introduced Into the Uterine Cavity, They Are Not Withdrawn Until Both Feet of the Baby Are Delivered.*—The practice of introducing one hand and then the other in an attempt to grasp the feet of the baby is to be discouraged be-

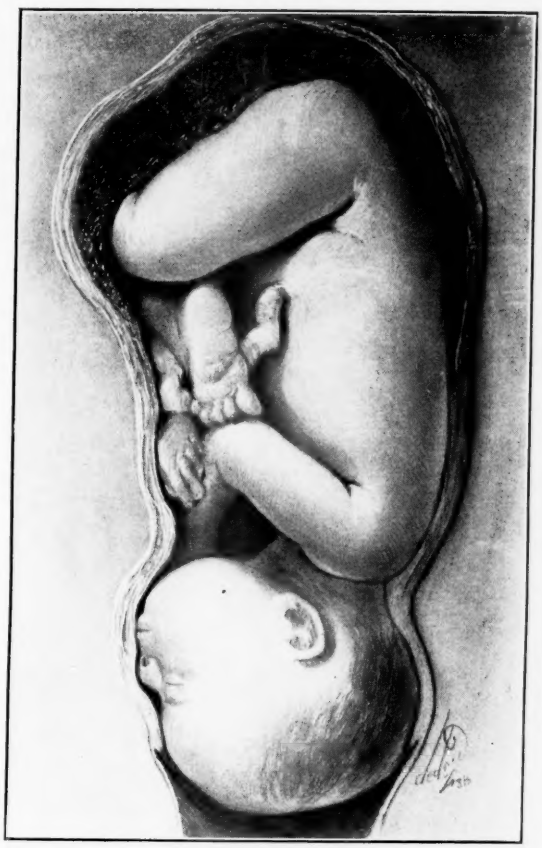

Fig. 4.—Impossible case for version and extraction.

cause of the possibility of infection. If difficulty is encountered in locating the second foot, slight rotation of the body of the fetus will aid the operator in discovering the lost foot.

5. *Never Proceed With an Internal Podalic Version and Extraction Unless the Operator Is Positive that the Arms of the Fetus Are Folded Across the Chest.*—We believe and teach, if the baby's arms have extended, the operator alone is to blame, because he either failed to fold

the arms or he did it carelessly. If there is an excess of amniotic fluid and the arms tend to float away from the folded position, it is a simple matter to allow some of the fluid to escape.

It is rarely possible for the arms to extend if they are folded across the chest, because the chin of the baby keeps them from being dislodged upward and the pressure of the uterine musculature aids in keeping them in place. The rather general idea that the arms are normally in that position is false (Fig. 5), and in many cases we find an arm either alongside the body or the head and any attempt to extract that baby with an arm or arms in those positions will invariably produce an extended arm or arms.

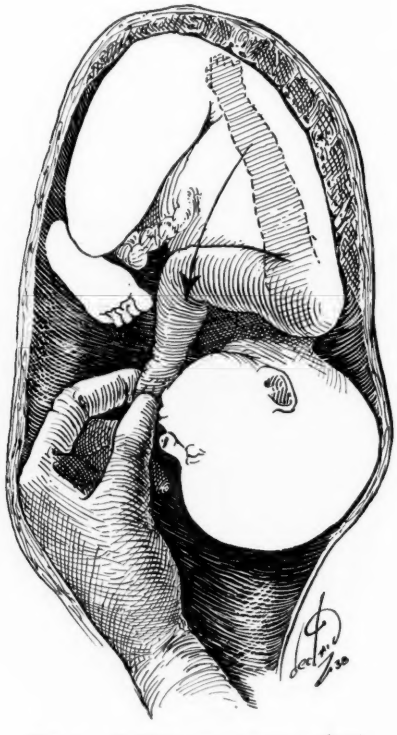

Fig. 5.—Folding arms across chest.

We feel this is so important that we now re-check the position of the arms before the legs are delivered, in order to be positive that the arms are in the proper position, before the version is attempted.

6. *Too Much Traction Should Not Be Exerted in the Delivery of the Feet.*—This warning is given because operators employ too much force in pulling on the feet and when the feet are delivered as far as the vagina, it is found impossible to complete the extraction.

The probable explanation is that the operator failed to feel the fetal head through the abdominal wall, and although he went through the motions of pushing the head up out of the iliac fossa with his external

hand, the head remained lodged in the iliac fossa and the position of the fetus might now be compared to a half-opened jackknife, the point of the blade representing the head and the tip of the handle the feet. Continued traction will certainly rupture the uterus unless the operator remembers to release his grasp of the feet entirely and explore thoroughly the interior of the uterus. He will invariably find the fetal head still lodged in the iliac fossa and if he will place the head in the hollow of his hand and push it up into the fundus, holding it there by his external hand, while he again grasps both feet, he will find that the legs can be delivered with ease (Figs. 6 and 7).

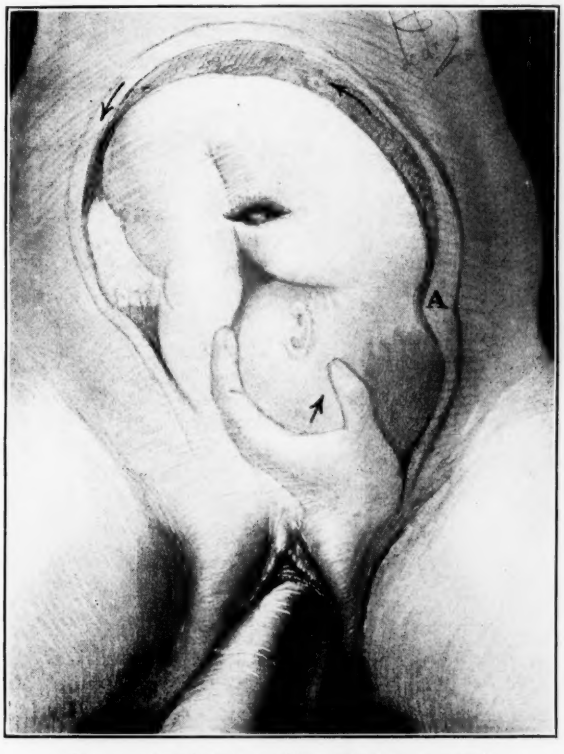

Fig. 6.—Jackknife position of head and feet.

7. *Avoidance of Arm Injuries Can be Accomplished by Doing Away with Pressure on the Upper Arm.*—It is pretty well agreed by all familiar with this subject that delivery of both shoulders in succession, as anterior shoulders, is a decided improvement in the extraction. This maneuver is accomplished by placing the finger at the angle of the scapula, after the scapula appears at the vulva and *not* in the axilla. At this point of the delivery, the scapula is pushed anteriorly under the pubic arch.

A serious fault which many obstetricians have is that after successfully delivering the shoulders, they invariably fail in the delivery of the arms and subject the baby to a possible paralysis of the humoral

nerve, by deliberately placing the index or middle finger on the deltoid region, and try to extract the arm by sweeping the finger downward and hooking it with considerable force around the humerus (Fig. 8).

Much easier and safer is the method of entirely avoiding the deltoid and humoral regions and delivering the arm by placing the finger directly in the bend of the elbow and then lifting the arm up over the chest like a pump handle, thereby avoiding nerve injuries and a possible fracture of the humerus.

Fig. 7.—Holding head in fundus with external hand.

8. *Avoid Excessive Traction in Delivery of the Aftercoming Head.*—It is not uncommon to see terrific traction exerted upon the neck of the baby in a hurried effort to deliver the head. The back of the baby, therefore, is bent too far upward toward the mother's abdomen. It is essential that flexion of the head and body be maintained at all times. The possibilities of fracture of the clavicles and injuries to the neck and head are great, if the operator forgets that it is much easier and much safer to push a head through the pelvis than pull it through. Omitting this precaution has led to the fracture of the neck of the baby and its death. Maintaining flexion of the head by pressure on the chin, moderate pressure from above and moderate traction from below provides a successful delivery.

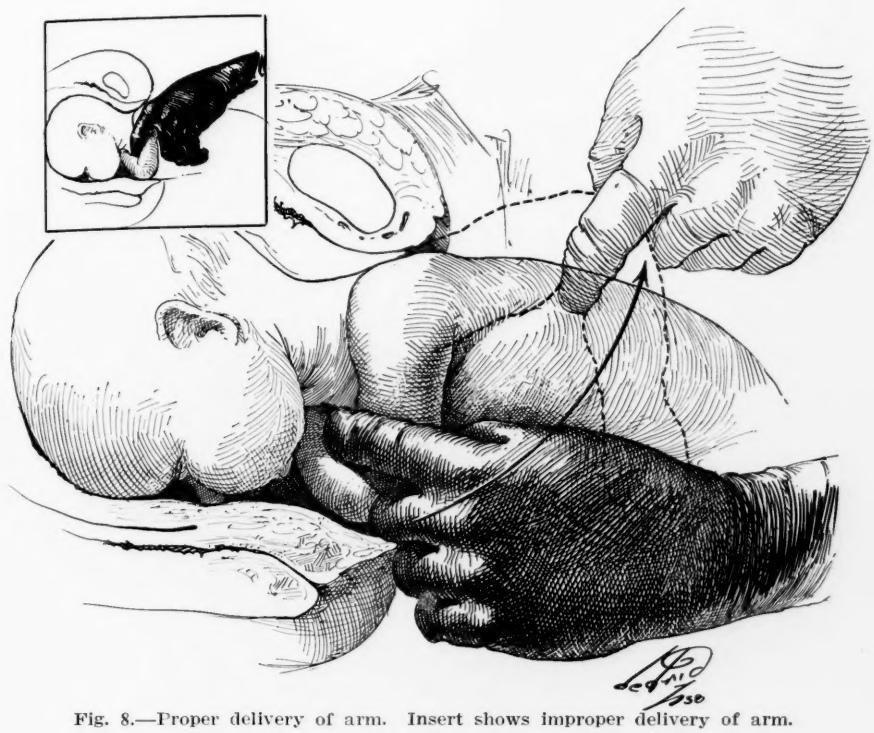

Fig. 8.—Proper delivery of arm. Insert shows improper delivery of arm.

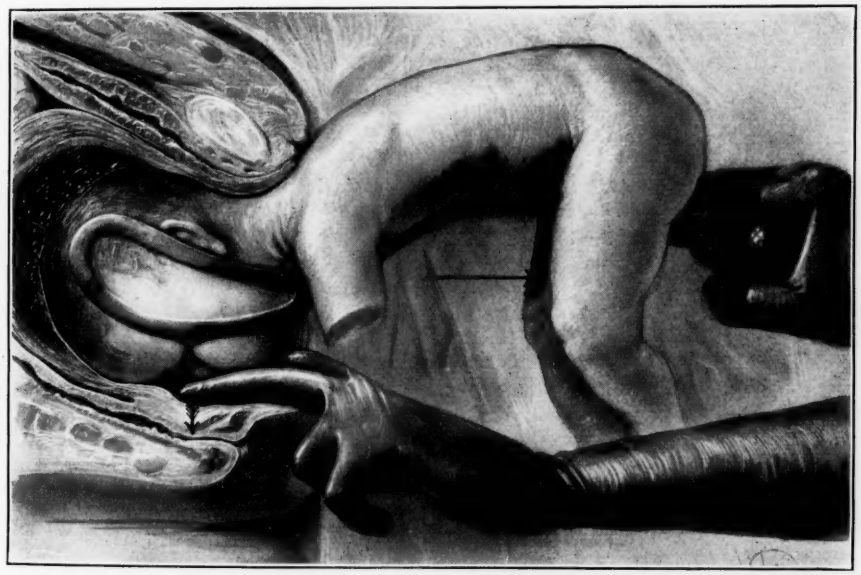

Fig. 9.—Pressure being exerted on perineal body when Piper forceps are used.

If, as sometimes happens, there is an unavoidable extension of the head which cannot be corrected by pressure of the operator's fingers on the chin, or pressure on the head from above, then the use of the Piper forceps is indicated.

9. *Never Attempt the Use of the Piper Forceps on the Aftercoming Head Which Is Not Well in the Pelvis.*—Too often the use of the Piper forceps is resorted to, when the head is either not in the pelvis at all, or is high in the pelvis. It is far better to push the head down into the pelvis as far as possible and then, if difficulty is encountered, to apply the Piper forceps to the sides of the head. The difficulty usually encountered is either a large or an extended head, which can be corrected by the proper use of the forceps. By that I mean flexion of the head can be increased by lowering the handles before locking the forceps (Fig. 9).

As the head descends, obstruction and resistance usually are encountered in the perineal body. The latter, if pressed down by the index or middle finger of the left hand, partially introduced into the vagina, will be depressed sufficiently to allow the chin to slide over it, thereby avoiding a lacerated perineum or the necessity of an episiotomy.

Occasionally in a flat type of pelvis, it is much easier to push the head into the pelvis if the head is grasped and rotated transversely by the external hand, thus making use of the largest diameter of that particular inlet.

And finally we are, at the present time, very prone to use Piper forceps on the small, premature aftercoming head, for we feel that trauma to such a head is minimized by the use of forceps.

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DISCUSSION

DR. BERTRAM H. BUXTON, PROVIDENCE, R. I. (by invitation).—In the last ten years at the Providence Lying-in Hospital in some 26,000 deliveries, there have been only 307 versions and extractions, about 1 in 80 deliveries. None of these is of the elective type, except for the delivery of the second of twins. The number has gradually decreased each year from 75 in the first year and a half, to 10 in the year 1937. This has resulted from the increase in the incidence of cesarean section, because we have recognized earlier in labor the case in which formerly version and extraction were resorted to after failure of high forceps.

The statement is made that "A version should never be attempted until the greatest circumference of the head is at least within the pelvic brim and has had a chance to mold." Given the premise that we are going to do elective versions, this is perhaps good advice, but to my unconverted mind a head already molded to come through as a vertex would be much easier delivered by forceps as a vertex.

In regard to the statement that, "if after a reasonable length of time the operator is unable to get both feet, he should then stop and proceed with another method of delivery," I should like to ask Dr. Potter what method he would then recommend. I would rather take a chance on delivery with one foot than to attempt a high forceps on a floating head or a cesarean section after so much manipulation.

DR. A. K. PAINE, BOSTON, MASS.—Some versions fail, not because the nondilatation of the cervix is unrecognized, but because the operator assumes that dilatation will complete itself easily during the delivery. These are errors in judgment rather than inability to recognize the nondilated cervix.

The precaution "never proceed with a version and extraction until the operator is positive the arms are folded across the chest," is of interest. It is further stated

that "Normally in 50 per cent of the cases, the arms are in some other position than across the chest, and extraction in such a case *invariably* produces an extended arm or arms."

In a normal breech delivery an extended arm is not very common unless the operator indulges in questionable procedures to hasten delivery. In versions and extractions as they are generally done surely an extended arm is not encountered in half the cases. By the Potter reasoning noncompliance with this precaution should result in prolapsed arms in approximately half the cases. That certainly is not the general experience.

As regards the importance of not applying force directly to the shoulder or humerus in delivering an arm, it has been my experience that if that downward traction on the body, which delivers the anterior shoulder, is continued long enough the arm will be spontaneously delivered in a large proportion of the cases. The same applies to the posterior arm after its rotation to the front. Digital delivery of the arm is reserved for those cases in which the above technique is not easily successful.

DR. T. L. MONTGOMERY, PHILADELPHIA, PA.—Considering the wide field in which the Potters apply version and the early stage of labor in which they institute it, it is doubtful that all the details of procedure which they recommend are applicable to the indications and conditions under which most of us select the operation, namely, in transverse position, prolapse of the cord, and some of the head presentations in which deflection or malposition calls for a corrective obstetric procedure.

If one is to perform elective internal podalic version and extraction upon all obstetric patients, then one can conceive of the advisability of manually dilating all cervices, starting the version before the membranes rupture, and seizing both feet of the fetus to perform the turning. Under normal indications, however, one is faced with conditions under which the membranes have ruptured, considerable amniotic fluid has drained away, and the uterus so firm that it is not always possible, feasible, or wise to attempt to reach both lower extremities. Under such circumstances it is often easier to deliver the posterior arm in the hollow of the pelvis than to attempt extraction of the anterior. I am of the opinion, therefore, that the old style of version is oftentimes better adapted to the peculiar circumstances of normal obstetric practice than are some of these manipulations recommended by Dr. Potter.

My own observations of the Potter version as performed by Dr. Potter himself are that the cervix is not always completely dilated or nearly so when version is undertaken, and that, therefore, the major portion of the dilatation must be accomplished by manual manipulation; second, that inasmuch as the version is done early in labor and before the membranes have ruptured, there is actually and practically no time for molding of the fetal head before the version is accomplished; third, that cesarean section is performed in many instances in which a better test of labor might have eventuated in normal head-first delivery; and fourth, that as an end result rupture of the uterus in subsequent pregnancies, with sacrifice of the fetus, is not uncommon.

While the Potters have perfected themselves in this form of version and evidently have few accidents, those who have endeavored to emulate their efforts in other cities have often met with disaster. In the records of our maternal welfare work in Philadelphia, there is no more depressing period than that during which a certain school of obstetricians undertook the Potter method of version in a high percentage of their deliveries. The same has evidently occurred in other cities.

This being the case, it would seem to me far more important to collect and report before this organization the maternal and fetal mortality that has resulted from the attempts to follow this form of obstetric practice than to lay further emphasis upon its technique. With such knowledge at hand we should be able properly to evaluate this procedure and doubtless relegate it to the position for which it is intended in obstetric practice—a serious operation to be performed only in the face of definite obstetric indications.

DR. GEORGE M. SHIPTON, PITTSFIELD, MASS.—This paper lays stress on the points to be brought out in case one has to do a version and extraction. While we

may not approve of this method of delivery as a routine method of procedure, the Potters have taught us more about the procedure than any one in the literature.

DR. ARTHUR H. BILL, CLEVELAND, OHIO.—Delivery through an undilated os is responsible for more trouble than any other mistake. This is true not only in versions but in any attempt to deliver a baby. I am opposed to manual dilatation except in an emergency. After my discussion of the breech cases yesterday, I was told that I might have given the impression that I advocated manual dilatation of the cervix. I wish to correct any such impression, for I am absolutely opposed to that in principle and simply said that what we call full dilatation in the case of a breech is not enough dilatation for the aftercoming head, and that when the breech has dilated as much as it possibly can, it may be necessary to iron out the cervix enough to remove any possible resistance to the shoulders and head.

Dr. Potter stressed folding the arms across the chest. Frankly I have never taken this seriously. I believe that the reason why the arms do not go up in his cases is not so much because he folds the arms over the chest as because he has the advantage of wonderful anesthesia with complete relaxation.

There are a certain number of cases in which the head will not enter the pelvic brim while in the abnormal position and yet will pass through very readily if in a normal position. In such cases, I think, I go a little bit further than Dr. Potter and perhaps do versions in some cases in which he performs cesarean sections. Therefore I would not say that the head must be through the pelvic brim and molded as a necessary preliminary to a version. While I do a great many versions, most of them are not prophylactic or elective versions but are to correct abnormalities, chiefly posteriors, occasionally face and brow presentations.

DR. IRVING W. POTTER, BUFFALO, N. Y.—This is not a paper on theory. It is a practical paper upon a practical subject in the field of obstetrics. The writer has had a very extensive experience in the management of cases of version and extraction and from his experience he has made the observations, which he has rounded into a paper. This paper was not on the indications for version, but it was an attempt to point out some of the dangers and pitfalls of a procedure that should be understood and is not understood.

We had many years ago an investigation that would satisfy almost any one. Early papers of mine were discussed, but they refused to print them until they had come to Buffalo and made an investigation. The Health Department looked over our records, and our maternal and fetal mortality were all investigated. I do not know how many times the Health Department called me up and wanted to know if they should let investigators go through the records. I said, "Certainly, we have nothing to conceal."

We have only tried to demonstrate the technique of version, and if you cannot regulate your indications that is not my fault, and if you cannot learn the technique that is not my fault. There is nothing personal about this.

DR. MILTON G. POTTER (closing).—This paper was not on indications for version and extraction and for that reason I will not at this time answer the many questions asked concerning indications. I repeat, this paper only attempted to present the pitfalls one may run into if at any time the operator felt that version was indicated.

THE RELATION OF URETERAL PAIN TO MENSTRUATION

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(From the Department of Gynecology, Syracuse University)

HUNNER[1] was the first to call attention to ureteral pain due to stricture. The slowness with which this was accepted is undoubtedly due to the fact that pathologic evidence was difficult to obtain, that x-ray studies fail to give concrete information and that in *uninfected* cases, of which there are many, *no abnormal elements are found in the urine.*

The etiology of ureteral stricture is also indefinite, there being some evidence that they are congenital and some that they are due to either focal infection or are a result of urinary infection early in life. Their existence in conjunction with stone leaves a question of which is cause and which is effect. However, those of us who have noted that thorough dilatation of the ureter has been instrumental in preventing recurrent stones feel that the stricture with its resulting stasis is a factor behind the formation of calculi.

Besides stricture, it is also quite likely that spasm of the ureter may cause pain. Wharton[2] has described the manner in which the sympathetic nervous system supplies the ureter and since intestinal and uterine spasm are conceded, it seems reasonable that a similar condition may occur in the ureter. *When we understand more thoroughly the behavior of the sympathetic nervous system we will better understand chronic pain.*

Accepting ureteral stricture and spasm as causes of pelvic pain, there need no longer be a confusion in diagnosis if disease of the appendix, tube, or ovary cannot be demonstrated. In fact, it should be pointed out that the ovary, so frequently accused, rarely causes pain except when it is the seat of an easily demonstrable pathologic condition. Neither is it necessary to have stone, infection, or tumor present in the ureter to produce pain, any more than that there must be some tangible pathology in the uterus to produce dysmenorrhea.

In choosing the following cases I have included only those in which the patient's primary complaint was painful menstruation. In fact, careful questioning was necessary to elicit the character of the pain and separate it from the usual uterine cramps. Let it also be emphasized that the ureter has not been the only obscure cause of pelvic pain. Cervical lesions, as suggested by Young[3] and by Sutherland[4] have also been noted. Patients with unsatisfactory sex life, notably those practicing interruptus coitus, may have, probably due to ovarian congestion, severe lateral pain at the menstrual period with negative pelvic findings.

The symptoms presented by patients suffering from ureteral spasm or stricture may be varied, but the important one is pain. This is similar in its location and radiation to the colic accompanying the passage of a

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stone but varies in severity and extent. It is usually described as a "boring pain" or a "dull hard ache" low in the side, and it may begin a week or ten days before the onset of the period and last with varying intensity until the flow is well established, or it may occur only just before or during menstruation. The pain is often referred to the ovary which may be tender to palpation thus leading to errors in diagnosis. Very often too, there is a frequency of urination, erroneously attributed to pressure of the engorged uterus upon the bladder. The presence of burning or pain on voiding depends on whether or not there is an infection.

The physical findings are few. The presence of one or more abdominal scars on a patient who still has the pain originally complained of is excellent indirect evidence that the trouble is in the urinary tract. There are three points of tenderness which lead to the impression that the ureter is at fault: First, the costovertebral angle, second, a point lateral to and below the umbilicus, where the ureter crosses the pelvic brim and a third, the area where the ureter enters the bladder.

The first is variable and its absence in no way eliminates the ureter. The second (Morris's point) where the ureter dips into the pelvis is somewhat more reliable. However, tender loops of bowel or even the anterior aspect of a painful sacroiliac joint may cause soreness at this point. The third region at the vesical end of the ureter, as palpated vaginally, is most important. This is reached by turning the examining fingers to the lateral portion of the anterior vaginal wall where the ureters converge to the trigone. If the ureter is the cause of the pain it should be tender at this point. Since the presence of tender loops of bowel in the pelvis may give false evidence, considerable advantage has been gained by the following procedure: The table is raised to a moderate Trendelenburg position with the head elevated enough for comfort; by a gentle upward stroking of the abdomen the pelvis may be thus freed of coils of intestine.

If gross disease of the pelvic organs has been found, its importance must be properly evaluated since some of these lesions cannot produce pelvic pain of the character described. The surgical removal of diseased structures although perhaps justified may have no effect upon the pain for which the patient has sought relief. The failure to realize that the absence of pus or blood in the urine does not always rule out the existence of ureteral stricture has led to many errors.

The final identification of the ureters as the cause of pain rests on cystoscopic examination. Testing with a bulbed catheter is probably the most satisfactory means of identifying stricture. The obstruction is located by the "hang" of the bulb as the catheter is withdrawn. The one procedure which leads most frequently to error is the relying upon the passing of the No. 6F ureteral catheter. This catheter will find only the most severe stricture or spasm, and negative findings by this method are worthless. In 1923 I[5] described a technique for ureterogram which is of help in locating strictures. Often, however, x-ray reveals no information. The obstruction to bulb or catheter and the identification of the character of the pain are the most reliable points in diagnosis.

In the treatment, gradual dilatation of the ureter up to a 14F or 16F is usually successful. This may be done with a bulbed catheter or a graduated bougie. When the obstruction is in the lower third of the ureter, the bougie works satisfactorily and seems to produce less trauma than the bulb. *In cases of true stricture the patient must be warned that contraction of the lumen may return and occasional future treatments be necessary.*

In cases of severe spasm unrelieved by dilatation, Wharton[6] reports success with an operation for completely denervating the ureter from a point opposite the third lumbar vertebra down to the bladder wall. This procedure gave partial relief in one of my cases and none in another.

From my records I have found 14 cases presenting the complaint of dysmenorrhea in which the pain was lateral and radiated along the course of the ureter. They naturally fall into three groups. In the first there are 3 patients. One, a girl, 15 years old, began to menstruate at the age of 13. Painful periods began one year later. Various remedies had been used and she was referred for cervical dilatation. However, the pain was on the left side and radiated down the inner aspect of the thigh. At cystoscopy a No. 6F catheter was passed easily into the left ureter and produced no pain. A No. 11F Gareeau catheter would pass only part way up the ureter, met considerable spasm, and it produced a pain identical with the one complained of. The ureter was dilated three times and all pain disappeared.

The other two patients in this group had pain on the right side and were relieved by dilating the ureter up to a 12F. It seems reasonable to suppose that the underlying cause in these cases was more a spasm than a stricture.

In Group 2 there are 8 cases. In 3 the pain was on the left side only, in 4 on the right, and in 1 it was bilateral. Four admitted some frequency or distress on urination and 4 had none. Three had had 2 operations each for the relief of the menstrual pain without benefit except that in one, "cramps and backache" were improved by a uterine suspension, although the pain in the side was uninfluenced.

The diagnosis of stricture in these cases was based upon obstruction to the ureteral catheter with or without bulb and the reproduction of the pain complained of. No hydronephrosis was found in any of them. Three received dilatation up to 15F, 2 to 14F, and 2 to 16F. In one, an early case, the dilatations were completed elsewhere and I do not know how large a bougie was used.

All reported as completely relieved except one. She was a very nervous and skeptical individual who had had two unsuccessful surgical attempts to relieve her pain. She had a very dense left ureteral obstruction which was dilated to 15F. She had eight months of relief for the first time since the onset of pain, but in spite of warning that she would need further dilatations if the pain returned, she refused treatment when this occurred.

In the third group are three cases which I will report in slightly more detail. The first is a single woman, aged 35 years, seen in January, 1931. Her complaint was severe pain in the lower left side appearing about a week before her period and continuing with increased severity until the flow began. It was aggravated by the presence of intestinal gas. There was also frequency and burning on urination. She had had a "chronic appendix" removed with relief of a right-sided pain. On examination, the pelvic organs were normal but the vesical end of the left ureter was tender and cystoscopy reproduced her pain. At this time as on several other occasions, edema around the ureteral orifices was noted. Many dilatations failed to relieve her. Consultations with internists, neurologists and psychiatrists failed to lead to a more definite diagnosis. Exploratory laparotomy in August, 1932 did not show any gross intra-abdominal pathology. At that time denervation of the left ureter according to Wharton's technique was done. The discovery of an elusive ulcer in 1936 and its treatment with phenol resulted in relief of the bladder distress, but the left-sided pain has never entirely disappeared, although it has been less frequent and less severe since the ureteral denervation.

This patient had numerous symptoms which were not always constant. Pain would occur in one side and again in the other or all symptoms might suddenly improve for no apparent reason. This, plus the fact that edema of the ureteral orifices was seen on several occasions, suggests the possibility that allergy plays a part in her trouble. This fits rather closely with the suggestions of Schwarz[7] and of Goodall[8] that dysmenorrhea in some cases may be due to this phenomenon. As far as I know, her allergy reactions have never been studied.

The second patient in this group was single, aged 24 years. For three years there had been a severe pain that radiated from the right kidney region along the entire course of the ureter. It appeared ten days before menstruation and lasted throughout the period. She had had the appendix removed without relief. On examination the pelvic organs were normal. The right kidney and ureter were tender. The ureteral catheter met marked obstruction and reproduced the pain. Dilatations up to 16F failed to give relief. Complete physical and mental survey by all departments failed to lead to a more definite diagnosis. A thorough exploratory laparotomy disclosed grossly normal abdominal and pelvic organs. Bilateral ureteral denervation was done. This likewise gave no relief. Besides these procedures the patient had received various hormone therapy without result. At my request the patient returned recently, stating that in March, 1938, she had been operated upon in another city, with relief of her pain. A report from the surgeon stated that after careful study, presacral neurectomy had been done but that the patient had told him she was not completely relieved.

This patient is particularly interesting. If the pain was of ureteral origin as its character seemed to indicate and *any* form of sympathectomy would relieve it, it would seem that complete ureteral denervation should have given at least a temporary good result. Since presacral neurectomy has been followed by marked improvement, it must be assumed that the ureter itself was not the cause of pain.

The third patient in this group, single, aged 27 years, was first seen in August, 1934. She had complained of severe dysmenorrhea with the usual uterine cramps accompanied by a persistent pain in the lower left side seemingly along the course of the ureter. She had had several operations resulting in the loss of her right ovary, appendix, and part of her left ovary. A suspension of the uterus and several dilatations of the cervix had been done and no relief was obtained. Catheterization of the left ureter failed to identify the patient's pain. However, its character seemed so typical that several ureteral dilatations were done but failed to cause improvement. Presacral neurectomy was followed by relief of the uterine cramps but the pain in the left side has persisted. It is very doubtful that the pain in this case was ureteral in origin. It would have been very interesting to have studied her before the function of her pelvic organs had been disturbed by so many operations.

COMMENT

The records of 14 patients whose chief complaint was painful menstruation have been presented. In each the pain differed from that of typical dysmenorrhea by occurring in the side and radiating along the course of the ureter. In 11, the fact that dilatation of the ureter resulted in relief indicates that the pain did originate in that organ. In 3 cases symptoms, although seemingly related to the ureter, failed to be influenced by dilatation. One of these was partially benefited by denervation. This patient also presented some evidence that allergy may play a part in her distress. One patient has obtained at least temporary relief from presacral neurectomy.

CONCLUSION

There are certain cases of dysmenorrhea in which the pain has an obscure and unusual origin. These require the most painstaking study, often needing the combined efforts of many branches of medicine. This should be recognized and surgery withheld until some definite procedure can be outlined.

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DISCUSSION

DR. HENRY D. FURNISS, New York City.—Ureteral stricture is a real condition, but it took the gynecologists a long time to convince the rest of the profession that this was so. The first one I discovered was by accident, in a patient who had previously been operated upon for a gall bladder condition. During her convalescence she had exactly the same type of attack for which the operation had been performed. Observation of a relationship between the pain of stricture and the menstrual period was made fifty years ago by Mirabeau. Whether the condition is due to some hormonal action or to ureteral congestion, I do not know.

Unexpected results have followed the dilatation of some of the strictures. One patient, for example, was freed of a diarrhea of several weeks' duration. Hunner has stressed this point and has reported relief of so many symptoms, seemingly entirely unrelated, that many are still skeptical. My experience has proved him to be right.

How these strictures form I do not know. We find ureteral orifices that are small and in no way the result of previous disease, so we must consider these of congenital origin. I believe that many strictures are due to an old cystoureteropyelitis, with subsequent narrowing of the ureter. The pyelitis may have been due to a congenital stricture of the ureter, as substantiated by the work of Meredith Campbell. At times, it is impossible to prove a stricture by either retrograde or intravenous urograms; yet the patient is relieved by ureter dilatation.

DR. W. A. COVENTRY, Duluth, Minn.—I would like to ask Dr. Sears if he can explain why these patients have pain immediately before menses and then after menstruation the pain ceases, and also whether these patients have any symptoms except during the time they are menstruating.

DR. J. P. PRATT, Detroit, Mich.—It is gratifying to hear Dr. Sears refer to the psychiatric aspects of ureteral and pelvic pain. He has indicated that spasm of the ureter is frequently responsible for the pain. What is the explanation of the spasticity? Definite organic causes are often easily demonstrated. More often, however, the cause of spasm is elusive. Stone, inflammation and tumor are definite terms readily understood. Emotional disturbance is not so easy to define but is no less potent as a cause of ureteral pain.

DR. SEARS (closing).—Dr. Furniss' experience with ureteral pain has been extensive, and I am pleased to have him join me in the plea for earlier recognition of this condition.

The only answer I have to Dr. Coventry's question is that through the sympathetic nervous system the hormonal changes in the blood at this time affect the ureteral muscle as they do that of the uterus. Ureteral pain, of course, may occur at any time, but I have chosen to report only the pains occurring in relation to menstruation.

I want, especially, to thank Dr. Pratt for emphasizing the psychogenic factor in pain, a point which I had time only to mention.

Any patient complaining of pain for which there is not an evident pathologic explanation, requires the most careful investigation. Some will be relieved by ureteral dilatation, some by very careful psychiatric investigation, and some by correction of cervical lesions. In some, sympathectomy will be followed by relief. Although this procedure is entirely justified at the present time, I believe the future will show that it will be possible to correct the condition which produces this spasm rather than dividing the nerves which carry the impulses.

BENIGN TUMORS OF THE CERVICAL STUMP FOLLOWING SUPRAVAGINAL HYSTERECTOMY*

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FIBROMYOMA of the cervical stump following supravaginal hysterectomy constitutes one of the unusual varieties of benign neoplasms. It occurs even less frequently than myoma of the vaginal portion of the cervix in intact uteri, which is also an uncommon condition. Much has been written on the subject of malignant tumors following operation, but since the first case of fibroma of the cervix was reported by Giles in 1923, only six additional case reports have appeared in the literature. The gynecologist apparently rarely encounters this condition, and it is only from the larger clinics that an occasional case is reported. In over 1,800 supravaginal hysterectomies performed at the New York Post-Graduate Hospital in the last eight years, but two cases of true fibroma of the cervical stump were found by other operators. These two, with two personal cases, form the basis of this presentation.

CASE 1.—Mrs. A. S., aged 49 years, was first seen by me in August, 1937, at which time she complained of pain in the right side of the abdomen and excessive flatulence of several years' duration. She gave a history of cholecystectomy and appendectomy sixteen years previously; both breasts had been removed for tumors; one five and one-half years, and one three years previously. Five years before, supravaginal hysterectomy, with prophylactic attention to the cervix, had been performed for uterine fibroids. The pathologic report of each of the tumors revealed no evidence of malignancy. Physical examination was essentially negative except for the four scars from the previous operations, one at the site of each breast amputation, and two on the abdomen. The cervix, however, was markedly eroded, hypertrophied, and bled easily when lightly traumatized. There were no palpable tumor masses. An immediate biopsy of the cervix showed chronic endocervicitis with no evidence of malignancy. The patient was advised to have the cervix removed as a prophylactic measure. She did not return for this, and was seen at irregular intervals up to March, 1938, at which time she had a severe vaginal hemorrhage. At the onset of bleeding, she was taken to an out of town hospital near her home, where treatment failed to control the bleeding. Four days later she was transferred to New York. When I saw her then, she appeared markedly anemic and somewhat exsanguinated. The cervix was very much enlarged, but the external os could not be identified. The bleeding seemed to come from the right lateral posterior aspect of the cervix, although the exact site could not be definitely determined. On bimanual examination, a tumor mass was found extending from the cervix into the pelvis, approximately the size of a large grapefruit. Because of the position of the tumor and the condition of the patient, it was felt that deep x-ray therapy might be beneficial. The roentgenologist, however, did not concur in this opinion. The patient was given several blood transfusions and treated conservatively, with a view to improving her general condition before operation. One month later, she again had a profuse vaginal hemorrhage. There was no change in size or consistency of the tumor mass, and again, the external os of the cervix could not be located, so the patient was prepared for operation. On opening the abdomen, widespread, dense adhe-

*Read at the Fifty-First Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, White Sulphur Springs, W. Va., September 22 to 24, 1938.

sions were found between the omentum, small intestines, and the tumor mass. The corpus of the uterus, ovaries, and tubes had evidently been removed at a previous operation. On freeing the adhesions, a tumor mass, the size of a large grapefruit was found originating in the cervical stump, extending downward into the cul-de-sac and recto-vaginal septum. The tumor was enucleated without difficulty, and the cavity tightly packed to control persistent oozing. Following the operation, a blood transfusion of 500 c.c. was given. Her progress was satisfactory up to the fifth day when she developed a left parotitis. Two x-ray treatments were given for this and the rest of her convalescence was uneventful. The tumor measured 10 by 9 by 7.5 cm., and was encapsulated by a tough fibrous membrane through which many dilated vessels were seen; on section, it was of firm consistency and pearly white in color. It was composed of interlacing bundles of smooth muscle fibers and fibroblasts between which were bundles of collagenous fibrous tissue. There were no areas of hemorrhage or degeneration.

CASE 2.—Mrs. A. D., aged 42 years, was first seen by me in June, 1932, at which time a supravaginal hysterectomy with retention of both tubes and ovaries was done for multiple uterine fibroids. At that time, the uterus was amputated just below the internal os by making a wedge-shaped excision, the cervix coned out from above, and touched with carbolic acid followed by alcohol. The pathologic findings were multiple intramural fibromyomas of the uterus with hyaline degeneration and chronic polypoid endometritis. The patient was well until March, 1937, at which time she complained of marked constipation, pain in the lower abdomen, and vaginal discharge of six months' duration. On pelvic examination, a hard mass, the size of a hen's egg which seemed to be attached to the stump of the cervix was palpated; it had the consistency of a solid tumor. At operation, a tumor mass was found extending into the right broad ligament, the pedicle being attached to the stump of the cervix. Except for considerable bleeding, it was removed without difficulty, and the patient made an uneventful recovery. On histopathologic examination, the tumor was found to be a leiomyofibroma.

CASE 3.—(Patient of Dr. Walter T. Dannreuther.) Mrs. M. M., aged 39 years, complained of vaginal discharge, pain in the left side of the abdomen and slight vaginal bleeding for the past year. Four previous abdominal operations had been performed, but the patient did not know what had been done. She had not menstruated since the first operation. She had previously had 4 children and several induced abortions. Examination revealed the presence of several tumor masses just above the cervix extending into the right iliac fossa. On opening the abdomen, dense adhesions were found and a group of tumors which had evidently grown in the cervical stump were demonstrated; both tubes and ovaries which had not been removed at any of the previous operations were removed with the fibromyomatous mass.

CASE 4.—(Patient of Dr. Thomas Cherry.) Mrs. R. G., aged 50 years, complained of vaginal bleeding for six weeks. A hysterectomy had been performed three and one-half years previously. Her menstrual periods had continued regularly for one year, but were of but one or two days' duration, and then ceased entirely. Six weeks previous to examination, she noted spotting, and complained of mild pain in the right flank, frequency of urination, urgency and partial incontinence. At operation, dense adhesions were encountered and a tumor mass 11 cm. in diameter, deep in the pelvis, originating from the stump of the cervix was found. This was adherent to the bladder, which had been pushed upward with the growth of the tumor. The pathologic examination showed a fibromyoma of the cervix with hyaline degeneration.

REVIEW OF REPORTED CASES

The first recorded case of benign tumor of the cervical stump is that of Giles in 1923, who referred to an unpublished case of Bruce-Porter. He removed a large fibromyoma from the cervical stump, five years after a subtotal hysterectomy for multiple fibroids, in a woman 39 years old. The condition was unique in his experience although he had performed nearly 1,000 hysterectomies, most of which were subtotal.

The following year, Reder reported a third case, one of myoma of the posterior cervical lip which was found three years after supravaginal amputation of the corpus.

Cleland's case was designated by him as a mucocele of the cervical stump, occurring fourteen years after supravaginal hysterectomy with removal of both tubes and ovaries for leiomyomas of the uterus; the cervix was in good condition at the time of the first operation. He was unable to give it a better name than cystic degeneration of the cervical stump.

Moench's case, reported in 1929, was of particular interest in that it was found six weeks following hysterectomy.

The largest benign growth was reported by Fletcher in 1935. Eight years after hysterectomy, he removed a fibroid from the cervical stump, weighing 12½ pounds, apparently subvesical in type.

Greenhill's case was also subvesical and the interval between the hysterectomy and the discovery of the tumor was the longest on record, seventeen years. The growth was entirely covered by the bladder on its anterior and posterior surfaces.

COMMENT

It is apparent that benign tumors of the cervical stump are predominantly fibroma. Histopathologic examination shows that their structure is essentially the same as those of the uterus or cervix. There are no demonstrable causes for fibromyomas, and some of the theories which have been advanced concerning their origin are open to serious question, especially in the light of certain factors present when they develop in a cervical stump. It has been contended that excessive ovarian activity causes a hyperplasia of the uterine muscle cells in local cellular areas with impaired circulation, but in many cases, hysterectomy and removal of the endometrial tissue had been performed several years before the appearance of the cervical tumor. Another theory has been that menstrual blood is forced back by a retrograde current, irritating the tissues and causing proliferative action. This is hardly tenable because many of these patients did not menstruate after the operation. The interval between the last menstrual period and the discovery of the tumor varied from six weeks to seventeen years.

Fibromyomas of the corpus are frequently multiple, but those of the cervix are usually single. A review of all of the available cases of those of the cervical stump reveals but one instance of multiple tumors. It is certain that tiny tumors may be overlooked and left in the tissue after fundal amputation. All of us have seen them and removed those which were macroscopically evident. It is interesting to speculate as to their outcome. Most must remain quiescent, in view of the small percentage developing in the cervical stump when so many hysterectomies are performed for fibroma of the uterus. Is it possible that one of these tiny tumors left in situ increases to such size as to necessitate operative intervention? And how can we account for the growth of but one?

There has been some diversity of opinion regarding the need of prophylactic treatment of the cervix at the time of hysterectomy, but the majority of surgeons advocate removal or destruction of the endocervical and endometrial tissue and glandular structures by excision, cauterization, or the application of high frequency current or chemical corrosives. Some adhere to a "leave alone" policy, whether the ovaries are removed or not. Others feel that an adequate amount of endo-

metrial tissue acts as a stimulus for normal glandular function when the ovaries are not removed. Is it possible that the eradication of this focus may account for the low percentage of tumors, benign or malignant, occurring in the stump? If this be so, how can we account for the fact that they do occur when prophylactic measures have been taken?

These tumors apparently grow more rapidly than those of the body of the uterus and may attain a considerable size. The majority originate in the posterior portion of the cervical stump and tend to grow backwards toward the cul-de-sac. They may be retroperitoneal, intraligamentary, or subvesical.

The first manifestations are usually obstructive, due to pressure of the growth—marked constipation, pain in the abdomen or pelvis, and if adhesions are present, drag on the adjacent viscera. With pressure on the bladder, the patient complains of urinary disturbance, urinary frequency, urgency, incontinence, or retention. Vaginal bleeding or discharge is frequently present; it may be slight or profuse. In one of our patients, the bleeding was so severe that immediate transfusion was necessary.

If the possibility of such a tumor is borne in mind, the diagnosis should not be difficult. It is based on palpation of a solid tumor attached to or in relation to the cervical stump. If the mass fills the pelvis, there may be some confusion as to the origin and type of tumor, particularly if the uterine adnexa have not been removed or dense adhesions are present. Due to the location of the growth and possible distortion of the ureters or bladder, a careful urographic study of the urinary tract should be made to determine the relation of these structures to the tumor before treatment is instituted.

Surgical intervention should be prompt. Because of the site of the growth and its tendency to grow upward and backward, the abdominal route offers the best method of approach. The operation may be difficult and tax the skill of the surgeon, as dense adhesions usually present may cause malposition, distortion or fixation of the adjacent structures. Once free, the tumor is easily shelled out. The possibility of distortion of the bladder from a previous operation or possible atypical position of the ureters should not be overlooked, and care must be taken in the identification, separation, and preservation of these structures. If the tumor mass is found so adherent to the bladder that separation cannot be accomplished without injury to the viscus, it is advisable to resect that portion of the bladder with the tumor mass, and repair the opening in the bladder wall. There is usually considerable venous oozing from the cavity from which the tumor is enucleated and this is best controlled by packing. All raw areas should be peritonized. It is gratifying to note that all of these patients recovered, despite the poor physical condition of some of them.

Our present knowledge does not permit of a logical explanation for the spontaneous development of these tumors, and it is only by a study of a much larger group of cases than is now available, that the true cause may be determined.

SUMMARY AND CONCLUSIONS

1. Benign tumors of the cervical stump are extremely rare.
2. Four new cases are presented, with a review of the literature.
3. Some of the etiologic explanations advanced for the cause of tumors of the uterus or cervix are obviously incorrect.
4. It is only by the study of a much larger group of cases than those now available that further light will be thrown on this subject.
5. The possibility of a benign cervical tumor should be borne in mind.
6. Early surgical removal is advised.

I wish to thank Drs. Dannreuther and Cherry for their courtesy in permitting me to report their cases.

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DISCUSSION

DR. LOUIS E. PHANEUF, Boston, Mass.—Dr. Hyams has brought to our attention what appears to be a very rare gynecologic condition. I, personally, have performed very close to 1,000 hysterectomies, a high percentage of which were supravaginal, and have not met this lesion, nor have I seen it listed in the records of the Carney Hospital for the past twenty-five years.

Dr. Hyams' case reports reveal an important fact, and that is that these neoplasms are handled better abdominally than they are vaginally. The close proximity of these tumors to the ureters and bladder, to which they may be adherent, would make the vaginal operation arduous and difficult in many instance, whereas by working abdominally, as has been pointed out, the danger of injury to these structures is greatly lessened.

DR. HENRY SCHMITZ, Chicago, Ill.—A review of our clinical records did not show a single instance of myoma in a cervical stump. The incidence of cervical location in uterine myomas is 8 per cent. However, the incidence of carcinoma in the cervical stump is 2.5 per cent in about 1,000 cases of cervical cancers.

In the first case reported by Dr. Hyams the patient, according to the report, was seen first in August, 1937, when a cervicitis was found. About seven months later, i.e., March, 1938, on readmission for severe hemorrhages, a tumor mass the size of a grapefruit was present extending upward to the right of the cervix. The histologic findings were those of a leiomyofibroma. I wonder whether microscopic re-examination of the tissue might not show the presence of large, atypical cells stamping the tumor a sarcoma, or the formation of numerous round cells dispersed within the myoma indicating a morphologic transition to sarcomatous degeneration, the so-called myoma malignum. Only thus could be explained the hemorrhages and the rapid growth.

It may be said that tumors appearing within one year after the operation were probably present at the time of operation. Moench reported such a tumor 11 cm. in diameter within six weeks after a subtotal hysterectomy.

The rarity of such tumors therefore should not contribute another factor to the controversy of total versus subtotal hysterectomy, if the cervix is normal at the time of operation. Such tumors should not be treated with radium or roentgen rays as they are invariably associated with pain either from pressure or inflammation.

DR WALTER T. DANNREUTHER, NEW YORK CITY.—I now have under observation two additional cases. One is a woman operated upon by myself sixteen years ago, in whom I did a high fundal amputation without coning out the cervical stump, and in whom I succeeded in preserving a miniature menstruation, which was important for psychologic reasons. About a year ago this patient returned complaining of symptoms other than those relative to the cervical stump, and I then found that she had a hard, round and symmetrical tumor, about the size of a hen's egg, involving the entire cervix. It is causing no local symptoms, and since she is now 49 years of age, I anticipate that with the onset of her menopause there may be a regression of the new tumor.

A second patient was operated upon five years previously by someone else, and in this instance there was no reason to attribute the symptoms, for which she consulted me, to a cervical tumor, despite the fact that such a tumor was quite evident. As this woman is also close to the climacteric period, and in view of the fact that the tumor is symptomless, I have not urged another operation. I can therefore include in my own experience not only the case cited by Dr. Hyams, but also two additional ones. The point I might emphasize is that there are cases of postoperative fibroid tumors of the cervix which do not produce either leucorrhea or hemorrhage.

DR. WILLIAM H. WEIR, CLEVELAND, OHIO.—An interesting condition was found recently in a young woman who had complained for two years of severe pelvic pain, lasting for two weeks of each month at the time of the period. This pain had not been relieved by supravaginal hysterectomy eight months previously. On examination a tumor about an inch in diameter and exquisitely tender to the touch was found to the right of the cervical stump and apparently adherent to it as well as to the base of the bladder. The surgeon who performed the hysterectomy said that the tumor was apparently not there when he operated. For this reason, and owing to the extreme tenderness of the mass, the possibility of its being an ovary adherent to the cervical stump was considered. However, an endometrioma seemed the most probable diagnosis. The tumor, together with the cervix, was removed through an abdominal incision. It was so intimately connected with the bladder that the two had to be separated by sharp dissection and a small tear in the bladder wall resulted. This was repaired but a tiny vesicovaginal fistula persisted. However, this was successfully closed from below a few weeks later. The tumor on section showed the typical gross and microscopic appearances of an endometrioma with small black hemorrhagic areas throughout it, and it was quite similar to one about the same size removed a few weeks later from the abdominal scar of a former cesarean section. A question arose whether this should be considered an adenofibroma of the cervix, since the two were so intimately connected, or an endometrioma that had happened to develop in close proximity to the cervix. The gland structure in the tumor being more of the corpus type, it was considered to be an endometrioma.

DR. NATHAN P. SEARS, SYRACUSE, N. Y.—I have seen four cases of tumors of the cervix, not all of them, however, occurring after the body of the uterus had been removed. One of them was a low-grade myosarcoma, another was a very rapidly growing sarcoma in the cervical stump. In the latter patient, who had had a hysterectomy for fibroids, the specimen had not been examined histologically but had been preserved, and later when sections were made, it was found that the original tumor was also sarcoma. The other two cases were benign.

DR. HYAMS (closing).—I agree with Dr. Schmitz, that in the first of my personal cases, the rapidity of growth of the neoplasm was highly suggestive of malignancy. With this possibility in mind, I was not content with the first pathologic report, and had the slides and specimens examined by a second pathologist.

Referring to Dr. Dannreuther's case, it is interesting to note that it was the only one in the entire series in which there were multiple fibroids.

INVERSION OF THE UTERUS WITH REPEATED HEMORRHAGES AND REPLACEMENT BY THE USE OF THE AVELING REPOSITOR*

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MRS. H. G., born in the United States, 19 years old, height 5 feet 3½ inches, weight 113 pounds. A blonde, pale young woman whose past history was negative.

She first reported to the prenatal clinic Oct. 5, 1936. Her last menstrual period was Aug. 20, 1936, her expected date May 27, 1937. Pregnancy was normal up to March 6, when she developed a mild pyelitis. She was admitted to the hospital and a culture of the urine showed *Staphylococcus albus*. The red cell count was 3,400,000, the hemoglobin 65 per cent, the white cell count 7,500. She was discharged after a three-day stay in the hospital. She reported regularly to the prenatal clinic and was admitted in labor on May 24.

After a labor of twenty hours she was delivered by low forceps because of a persistent occipitoposterior position. A left mediolateral episiotomy was repaired. There was a moderate amount of bleeding and the placenta was delivered spontaneously after a third stage of twenty-one minutes. This was followed immedi-

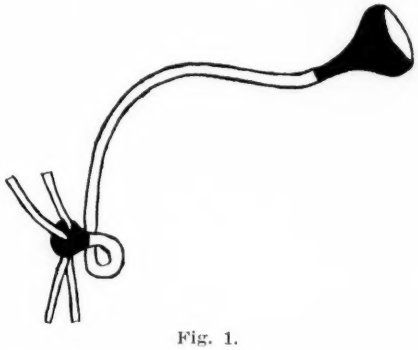

Fig. 1.

ately by a large amount of bleeding estimated at 1,000 c.c.; for this the lower uterine segment and vagina were packed. The cervix was examined and no laceration found, thirty minutes later the patient went into shock, acacia solution and two transfusions were given in rapid succession with little effect.

The patient was put on the table again, at which time a complete inversion of the uterus was discovered. This could not be replaced easily so the vagina was packed tightly with iodoform gauze, which stopped the bleeding. In the ensuing eight hours 1,100 c.c. more of blood were given, making a total of 2,200 c.c., since the delivery of the patient.

On May 29, five days after the inversion, under cyclopropane anesthesia, an attempt at reduction of the inversion was made with no success. Periodic bleeding resembling menstruation developed, and she was never in a condition where operation could be considered. The patient was several times on the danger list and, except for continued transfusions, would probably have died. In addition to this she ran a septic temperature for a long time. Of the many operative measures for her

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relief, such as Spinelli's operation, replacement by operation through the abdomen or vaginal hysterectomy, none could be considered because of the serious condition of the patient.

Reported series of cases treated with the Aveling repositor showed no mortality; it seemed that this method was at least worth a trial. This instrument could not be obtained from any of the surgical supply houses and the one used in this case was improvised from a pessary used for third degree procidentia. On September 6, or over three months after the inversion, the cup of the repositor was placed against the fundus of the uterus, upward and inward pressure was instituted by the use of four pieces of rubber tubing attached to the stem of the repositor and in turn to a belt about the patient's pelvis. On September 7 the patient had a chill and a temperature of 102.6° F., and on September 8 her temperature was 104°; there was a foul vaginal discharge. It was noted that the sigmoid stem was at a distinctly different angle and had shortened, there was a corresponding laxness of the rubber tubes, the fundus of the uterus with its retained repositor cup was felt through the abdominal wall at the level of the umbilicus. A vaginal examination disclosed the uterus reinverted and the cervix grasping the stem of the repositor tightly. Traction over a pulley on the foot of the bed with a one-pound weight was put on the stem, and the repositor came out about five hours later.

The patient was discharged on December 22, after a hospital residence of 212 days. The delay in her recovery after reposition of the uterus was due, in part, to slow healing of a sacral ulcer and also to her inability to walk because of long confinement in bed.

I believe that this case should be reported for two reasons: first, to demonstrate the absolute necessity, in cases of severe hemorrhage, for massive transfusions (2,200 c.c. in twenty hours); second, to call attention to the value of a simple procedure which is free from serious consequences and which may obviate the necessity for operating on cases of inversion of the uterus, which have resisted simple replacement, namely, the use of the Aveling repositor, which while it may not effect replacement in all cases, nevertheless, is worth a trial. There is no mortality due to its use. Furthermore, it leaves the uterus intact for future childbearing. All of the operative procedures have a definite and not inconsiderate primary mortality.

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26 South Goodman Street

THE EFFECT OF ESTROGENIC HORMONE ON THE H-ION CONCENTRATION AND THE BACTERIAL CONTENT OF THE HUMAN VAGINA, WITH SPECIAL REFERENCE TO THE DÖDERLEIN BACILLUS*

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SINCE the discovery by Döderlein (1892) of the gram-positive, non-sporing, acid-tolerating bacillus which frequently inhabits the vaginal tract of individuals of all ages, much attention has been focused on this organism, first, with respect to the rôle which it has been assumed to play in resistance to infection in the female genitalia by reason of its antibiotic properties, and second, as a therapeutic agent, since, when introduced into the vagina in a suitable menstruum, it was found able to grow and produce sufficient acid to inhibit the other common bacterial inhabitants of this organ. Much controversy has arisen among workers in the field as to the exact part which this organism plays in the production of acidity in the vagina. Döderlein assumed that it is responsible for practically all of the acid present. Many workers since Döderlein have gathered data which indicate a definite correlation between low pH of the vaginal secretions and large numbers of the Döderlein organism present in them. There have been others, however, who have thrown some doubt on the importance of this bacillus in the production of acidity, claiming that it could not attack the carbohydrate, glycogen, occurring normally in the vaginal mucosa.

It has been shown by many that there is a change in the H-ion concentration of the vaginal secretions with alteration in the ovarian activity of the individual. Thus, before puberty the pH ranges between 6.8 and 7.2 and the Döderlein bacillus is present in only a small number of the members of this group. During adult life, while the ovaries are actively functioning, the pH is lower and the aciduric bacillus is present with greater frequency than at the younger age. The Döderlein bacillus is present in 60 to 70 per cent of gravid individuals, the pH being markedly depressed, often reaching a level as low as pH 4.0 to 4.2.

While many have shown that this relationship exists, it could be arrived at only indirectly by inference that this correlation depends on the function of the ovary. It remained for Miura (1928) to furnish the first direct proof that the glycogen of the mucosa, the bacterial flora of the vagina, and the H-ion concentration were dependent on the activity of the ovaries. He studied the vaginal secretions of a number of individuals before and after ovariectomy, and was able to show that while a low pH and large numbers of the Döderlein organism were present be-

*Thanks are accorded Parke, Davis and Company for generous aid in supplying theelin for use in this work.

fore operation, this condition was completely reversed after removal of the ovaries, a change which was accompanied by the disappearance of glycogen from the vaginal mucosa. Cruickshank and his co-workers (1934) and the German school are in complete agreement with Miura's observations that the Döderlein bacillus is the most important agent for the production of acidity in the vagina, although they assume that some nonbacterial agent capable of breaking down the glycogen of the vagina into acid must exist.

Although no one can doubt the close relationship between ovarian secretion, the state of glycogen deposition in the vaginal mucosa, and the H-ion concentration of the secretions, some doubt has been cast on the mechanism of production of the acidity.

Schroeder and others (1926), and Miura and others have shown that the vaginal bacillus cannot break down glycogen to acid in the test tube. Kienlin (1926) demonstrated that appreciable quantities of lactic acid are present in the secretions of the vaginal tracts of newborn infants before any bacteria have as yet invaded the organ. This evidence points to the presence of some other agency in the vagina which is capable of producing large amounts of acid from glycogen, and serves to cast some doubt on the Döderlein bacillus as the most important agent in the production of the low pH levels which may be found.

It was the purpose of the work reported here to attempt to induce a high H-ion concentration in the vaginal secretions of human subjects and to study the bacterial content of this organ while the changes in pH were taking place. Since it has been shown by Hall and Lewis (1936) in monkeys, and by Lewis and Weinstein (1936) in children, that the parenteral administration of estrogenic hormone increases the H-ion concentration of vaginal secretions, human subjects were treated with this substance, and the changes taking place noted. Individuals in the postclimacterium who lacked Döderlein bacilli in the vaginal tract, and in whom the H-ion concentration was about pH 6.8 to 7.2 were chosen as subjects for the experiment.

MATERIALS AND METHODS

A complete history was obtained in each instance, and only individuals lacking evident disease of the genital organs were included in the study. Three observations were made in each case at weekly intervals before treatment was started, cultures and H-ion determinations of the vaginal secretions being made. One specimen of the vaginal mucosa for histologic study was obtained from every patient before the experiments were started. The estrogenic hormone was injected once a week in three consecutive doses; it was given in oil, 10,000 I.U. in each dose.

With the patient in the lithotomy position, a sterile speculum was inserted into the vagina and some of the secretion drawn up into a small pipette capped with a rubber bulb. In many instances, before injection of the hormone was started, there was a marked paucity of vaginal secretion; in such instances, the vagina was washed out with a very small amount of sterile saline solution (about 1.0 c.c.) and H-ion determination was carried out on this material. The pH was determined by the use of colorimetric indicators: bromthymol blue for the range 6.0 to 7.6, bromeresol purple for the limits 5.2 to 6.8., and bromeresol green for the range 3.8 to 5.4. Although this method of carrying out pH determinations is open to criticism on the ground that it is not accurate within 0.2 of pH unit, the changes which were considered significant were always of a much greater magnitude, and any error in the

method was thus reduced to a minimum. Furthermore, since the same method was always used, figures which were significant from a comparative standpoint were obtained, any inherent error in the method being constant.

The cultures of the secretions were made by swabbing the vaginal walls with a pair of sterile cotton swabs, immersing these in sterile saline solution and culturing within two hours on the tomato-yeast-peptonized milk medium of Weinstein, Weiss, Rettger and Levy (1933). This medium had previously been shown to be very efficient in growing organisms of the Döderlein type, endowing them with a colonial morphology (rough, fuzzy colonies) which made their recognition in a pour plate very simple. All cultures were incubated at 37° C. in an atmosphere of carbon dioxide and air for forty-eight hours, and then examined for the typical colonies, counts being made wherever the Döderlein organism was present to determine the relative frequency of this organism, as compared to the other bacteria in the vaginal secretions.

Sections from the vaginal mucosa were taken once a month for histologic study. These were fixed in formalin, stained according to the conventional methods, and then examined to determine the stage of development of the vaginal mucosa as a check on the effect of the hormone, and in an attempt to correlate these data with the findings of the cultural and pH determinations.

Cultures and pH readings were made for three weeks before the injection of hormone was started and every week after the beginning of the therapy, wherever this could be done. In some instances weekly specimens were not obtainable, but determinations were carried out with great enough frequency to make the results obtained significant.

RESULTS

As can be seen from Table I, the pH, which in every case was close to 7.0 at the outset, fell shortly after administration of the hormone to fairly low levels. In one case only was there no appreciable increase in H-ion concentration following the injection of the estrogenic substance; this individual (Case 7) had been subjected to ovariectomy and had been receiving hormone for one year prior to this study. All of the other individuals were in the natural postclimacterium and had not been treated previously. The average decrease in pH following the injection of 10,000 I.U. of the hormone was one pH unit. Further injections reduced this level still lower in most cases, pH 5.0 being not unusual. In several instances H-ion concentrations of pH 3.8 to 4.8 were observed. The findings in these individuals substantiate the results obtained by Hall and Lewis in monkeys, and by Lewis and Weinstein in young children following administration of the estrogenic hormone.

Following cessation of treatment, the pH tended to remain low in most instances: it returned slowly in some cases to a level closely approximating that present before treatment was started. In some individuals the H-ion concentration did not return to that observed before the experiment was begun. No explanation for this phenomenon is at hand.

The table indicates clearly that in 7 of the 9 individuals studied, the Döderlein bacillus was not present in detectable numbers during any part of the investigation. In spite of the fact that the vaginal secretions became very acid, this organism, which has been thought to be responsible for much of the acid in the vaginal secretions, could not be demonstrated.

Two of the patients harbored the Döderlein bacillus during the course of this investigation. In Case 6 it was present at pH 6.8, and at pH 5.8 to about the same extent. Later in the study, this bacillus was not present at pH levels as low as 5.0. There seemed to be little if any correlation between the degree of acidity and the presence of the vaginal bacillus in this individual. This observation receives further emphasis when Case 7 is considered. Here, large numbers of the aciduric organism were present in the vaginal secretion when the H-ion concentration approached the neutral point or even slightly exceeded pH 7.0 (pH 6.8 and pH 7.2). In fact, in this individual the organism could be detected at one time at a certain pH level, and one week later could *not* be demonstrated in the secretions of the same H-ion concentration.

TABLE I. H-ION CONCENTRATION AND DÖDERLEIN BACILLUS CONTENT OF VAGINAL SECRETIONS OF INDIVIDUALS TREATED WITH ESTROGENIC HORMONE

DATE	CASE 1		CASE 2		CASE 3		CASE 4		CASE 5		CASE 6		CASE 7		CASE 8		CASE 9	
	pH	% DÖD.	pH	% DÖD.	pH	% DÖD.	pH	% DÖD.	pH	% DÖD.	pH	% DÖD.	pH	% DÖD.	pH	% DÖD.	pH	% DÖD.
1/11	7.2	0	6.8	0	7.0	0	6.8	0	7.0	0	7.0	95	7.2	60	6.8	0	7.0	0
1/18	7.0	0	6.8	0	7.2	0	7.0	0	6.8	0	6.8	90	7.0	30	7.0	0	7.2	0
1/25	7.2	0	6.6	0	7.0	0	7.0	0	6.8	0	7.0	70	7.0	0	6.8	0	6.8	0
2/1	7.2*	0	6.6*	0	6.8*	0	6.8*	0	6.8*	0	6.8*	95	7.0*	90	7.0*	0	6.8*	0
2/8	6.0*	0	5.6*	0	6.6*	0	–	–	–	–	5.8	95	–	–	6.2*	0	5.6*	0
2/15	6.0*	0	5.6*	0	5.2*	0	7.2*	0	6.8	0	5.8*	95	7.2*	10	5.6*	0	5.0*	0
2/25	5.8	0	5.0	0	6.0	0	6.0*	0	7.0*	0	–	–	6.8*	95	5.0	0	5.2	0
3/1	5.0	0	4.8	0	–	–	4.8*	0	5.4*	0	5.8*	0	6.6*	0	4.6	0	5.0	0
3/8	6.8	0	5.8	0	4.8	0	3.8	0	3.8*	0	–	–	–	–	5.2	–	5.6	0
3/15	7.2	0	5.2	0	6.0	0	5.4	0	–	–	6.0	–	–	–	5.6	0	–	–
3/22	7.2	0	5.0	0	6.2	0	5.8	0	5.0	0	Menses	–	7.0	0	5.2	0	6.0	0
3/29	6.8	0	5.0	0	5.0	0	6.0	0	4.8	0	–	–	7.2	0	–	–	–	–
4/5	7.0	0	5.8	0	5.0	0	6.6	0	5.4	0	–	–	7.2	0	6.0	0	6.2	0
4/19	7.2	0	5.8	0	–	–	5.4	0	5.2	0	6.2	95	6.8	0	–	–	–	–
5/3	7.2	0	–	–	5.4	0	6.8	0	–	–	5.0	0	6.8	0	–	–	6.8	0
6/7	7.2	0	–	–	5.6	0	6.0	0	–	–	6.6	0	7.2	0	6.6	0	6.4	0
6/28	7.2	0	5.6	0	6.0	0	–	–	5.8	0	6.8	90	7.0	0	6.8	0	6.6	0

*10,000 I.U. of theelin injected intramuscularly.

Histologic study of the vaginal mucosa before and after treatment with the estrogenic hormone showed a definite correlation between the appearance of the tissue and the H-ion concentration of the secretions. Before treatment was started the pH was close to the neutral point and the mucosa was thin and revealed no evidence of active growth. Following administration of the estrogenic hormone, growth of the mucosa occurred with a corresponding increase in H-ion concentration. Sections taken at low pH levels showed many layers, and strong evidence of activity of the stroma. With cessation of treatment and a return of the H-ion concentration toward the neutral point, the vaginal mucosa again became thin and resembled that found before the experiments were begun.

SUMMARY AND DISCUSSION

Estrogenic hormone administered parenterally is capable of increasing the acidity of the vaginal secretions in cases where the pH is close to the neutral point before treatment. This change can be brought about *without* the intervention of the Döderlein bacillus, a fact which seems to be in direct contradiction to the claims of Cruickshank and others who attribute most of the acid present in the vagina to the activity of this organism. The data presented above show very little, if any, correlation between the degree of acidity of the secretions and the presence or absence of the aciduric vaginal bacillus, in spite of the fact that bacteriologic examinations of the vaginal secretions of individuals in different age groups seem to show a definite relationship between the frequency of occurrence of this organism and the state of activity of the ovaries which is directly related to the H-ion concentration of the vaginal secretions.

On the basis of the evidence obtained, the production of acid in the vagina seems to depend mainly on the state of activity of the ovary. The ovarian function determines the amount of glycogen present in the vaginal mucosa. This glycogen is probably broken down directly to acid by enzymatic action, as shown by Kienlin's finding of acid secretions in young infants in whom the vaginal tract is sterile; or it may be broken down to glucose by means of enzymes, and this carbohydrate then attacked by the bacteria present in the vagina. Such a theory for the formation of acid does not require the presence of the Döderlein organism, since most of the other bacteria present normally, such as staphylococci, diphtheroids, etc., may attack glucose, with acid formation. The activity of these organisms at low pH levels may be explained by the observation that staphylococci, streptococci, and diphtheroids are frequently found to be viable in the vagina at pH levels below those which limit their growth in the test tube.

Since it has been shown that large amounts of acid can be present in the vaginal secretions without the intervention of the Döderlein bacillus, the use of this organism as an indicator of the state of acidity and health of the vaginal tract seems unwarranted. The application of this organism in a suitable carbohydrate menstruum as a therapeutic agent in the treatment of various types of vaginal infections also seems questionable since large amounts of acid can be produced by the administration of the estrogenic hormone without resorting to the difficult manipulations involved in the preparation of cultures for insertion into the vagina.

CONCLUSIONS

1. The administration of estrogenic substance to individuals in the postclimacterium increases the H-ion concentration of the vaginal secretions.

2. There seems to be no definite correlation between the degree of acidity of the vaginal secretions and the presence or absence of the Döderlein bacillus. A corollary to this is that there seems to be little, if any, relationship between the amount of glycogen present in the vaginal mucosa and the presence or absence of the Döderlein organism.

3. The mechanism for the production of acidity in the vagina may be a dual one, enzymatic and bacterial, the organisms involved being any of the members of the normal bacterial flora which can attack glucose, with the production of acid.

4. The use of the Döderlein bacillus as an indicator of vaginal acidity and health or as a therapeutic measure in the treatment of vaginal diseases by virtue of its acid-producing powers seems questionable.

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BRENNER TUMORS OF THE OVARY

A Clinical and Pathologic Study of Ten New Cases With a Brief Review of the Literature

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HISTORICAL

In 1908 Brenner described three solid ovarian neoplasms occurring among elderly women. Grossly his specimens resembled fibromas but, microscopically, he found scattered islands of squamous epithelial-like cells in a dense stroma of connective tissue. He called the tumor "oophoroma folliculare" but it has since come to be known by the name of this early investigator.

Following this original contribution isolated reports of cases were added. In 1931 Robert Meyer was able to bring to 23 the number of reported examples, a number which had grown to 45 when Bland and Goldstein reported their case in 1935. The literature now contains approximately 70 examples of this newcomer in gynecology.

HISTOGENESIS AND PATHOLOGY

Three hypotheses have been advanced in an effort to explain the origin of these tumors. Meyer, who found in the serosa of Fallopian tubes tiny nests of "Brenner cells" favored the hypothesis of Müllerian metaplasia. Schiller postulated a dislocation of epithelium from the primary urogenital connection. The third hypothesis, namely, that these tumors arise through a one-sided development in a teratoma is based on their frequent association with pseudomucinous cystadenomas.

Brenner tumor is almost always unilateral. Grossly it resembles a fibroma, being whitish in color, and the solid variety is dense and hard. In another group the tumor appears as a solid nodule arising in the wall of a cyst.

Microscopically, the picture is uniform and consists of islands of squamous-like epithelial cells in a dense stroma of fibrous tissue. The peripheral rows of these cells are frequently arranged in palisades. Some of the islands are cystic with an inner lining of columnar mucous-producing cells. Mitotic figures are not observed.

The tumor is to be distinguished from granulosa cell neoplasm and from metastatic squamous-cell epithelioma. This distinction is simply made with the Galantha stain for mucus.

CLINICAL FEATURES

The clinical features of Brenner tumor are those of a slowly growing pelvic neoplasm with none of the usual features of clinical malignancy. Sixty per cent of the neoplasms occur after the menopause.

MATERIAL FOR STUDY

In a study of solid ovarian neoplasms removed surgically at the Mayo Clinic from 1905 to 1937, 10 examples of Brenner tumor were encountered. An analytical study of the clinical histories and pathologic data is presented.

REPORT OF CASES

CASE 1.—A white multipara, aged 46 years, presented herself for examination Sept. 25, 1936, because of a tender lump in the left side of the abdomen. Her family and personal histories were essentially negative. Menses always had been regular until one year prior to admission when, following five months of scanty flow, the periods ceased. Concomitant menopausal "hot flushes" had been noted. Nine months prior to registration she had noticed a firm, tender mass in the lower part of the abdomen. This, together with intermittent vaginal discharge, had caused her to consult a physician who found an ovarian tumor.

Examination revealed a large, firm tumor in the left side of the pelvis and abdomen. There was also marked cystocele and rectocele with an infected cervix. At operation, on Sept. 26, 1936, perineorrhaphy, total abdominal hysterectomy, and bilateral salpingo-oophorectomy were performed with removal of a solid ovarian neoplasm. The postoperative course was uneventful, and the patient was discharged from the hospital on the seventeenth postoperative day.

On pathologic examination, the right ovary was atrophic. Nothing remarkable was noted concerning the uterus except for a cystic condition of the cervix. The left ovary, containing a large corpus luteum, was seen at the lower pole of a solid,

fibrous tumor. The tumor measured 10 by 10 by 8 cm. The smooth surface was lobulated and contained a network of large veins. On section, this mass imparted a gritty sensation, the cut surface being hard and fibrous, not unlike fibroma. No cysts were seen.

Microscopically, the tumor was typical of the Brenner type. Scattered here and there in a dense fibrous stroma containing calcium, were islands of pale-staining epithelioid cells with distinct outlines. These islands were surrounded by a rim of darker staining, condensed stroma. The peripheral layers of cells occasionally were arranged in palisades. Many of the islands had cystic centers and, in some of these spaces, pink staining masses containing epithelial debris were seen. Lining these cysts, the cells of the tumor were arranged in a definite layer suggestive of secreting epithelium. Under high magnification, islands were seen to be composed of large, pale-staining cells with sharp outlines and vacuolization of the cytoplasm. The nuclei were small and the nucleoli relatively pinpoint in size. The cells in the cystic spaces appeared to be desquamated from the lining layer. Transition from normal ovarian elements could not be traced. The corpus luteum was seen to be old and organized and there was a definite capsule between it and the substance of the tumor. Follicles could not be found in either ovary. Stains for fat were negative, but the Galantha mucin stain demonstrated the presence of mucus in some of the cystic cavities.

The interesting feature, in this case, is the presence of corpus luteum in association with the tumor which shows that ovarian function to this extent was not affected. This finding has not been observed in cases of granulosa cell tumor which produces temporary sterility, and points to a different origin of the two types of neoplasm. The presence of amenorrhea could be well explained on the basis of the climacterium, a feature indicated by the associated menopausal symptoms. Leucorrhea and the occasional spotting observed probably could be explained on the basis of cervicitis, a feature which led the surgeon to perform hysterectomy rather than local resection of the tumor. The presence of calcium in the substance of the tumor represents an additional feature of interest (Figs. 1, 2, and 3).

CASE 2.—A white woman, aged 70 years, sought medical advice because of prolapse of the uterus of approximately ten years' duration. Her family and personal histories were essentially negative. She was the mother of five children. The climacterium occurred at the age of 51 years and was without incident.

Her present symptoms took the form of a bearing-down sensation in the pelvis which had been progressive in severity over the period of three months prior to her registration and she had noted, in addition, a slight mucoid vaginal discharge, at one time blood tinged.

Examination was essentially negative except for the presence of uterine prolapse with cystocele and rectocele and, on pelvic examination, the additional finding of a hard, movable tumor of the right adnexal region. At operation on April 17, 1936, anterior colporrhaphy and perineorrhaphy, abdominal hysterectomy, and right salpingo-oophorectomy were performed for prolapse and for a fibroid tumor of the right ovary. The postoperative course was uneventful and the patient was dismissed on the fifteenth day. She was living one and a half years after operation.

Examination of specimens removed at operation revealed a senile type of uterus with atrophic endometrium and considerable fibrosis of the myometrium. The right tube was the site of a small hydrosalpinx, and it was stretched out over the surface of a hard, white, lobulated tumor 6 cm. in diameter, replacing the right ovary. This tumor was cut with considerable difficulty and was like ordinary fibroma except for being darker in color and coarser in texture. No trace of normal ovary could be found.

Microscopically, the tumor was so similar to that of Case 1 that little additional description is necessary. Again, the picture was one of islands of epithelial-like cells with a dense surrounding investment of connective tissue, frequently with cystic centers. The stroma was coarse and fibrous and gave the impression of benignity and slow growth. Mitotic figures were not observed.

Fig. 1.—(Case 1.) A large solid Brenner tumor of the left ovary removed at operation. Note the corpus luteum at the lower pole of the tumor.

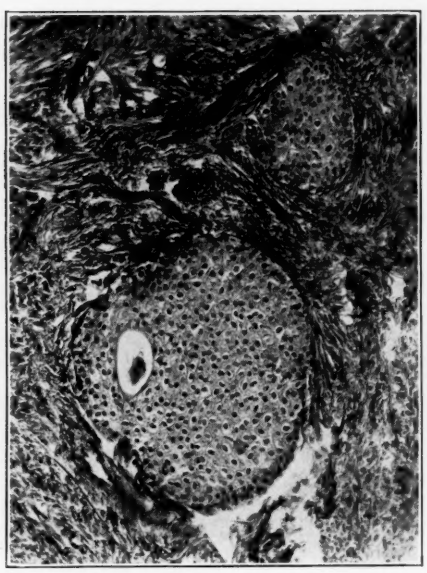

Fig. 2.

Fig. 3.

Fig. 2.—(Case 1.) Two islands of epithelial cells situated in a dense stroma. (×130.)

Fig. 3.—(Case 1.) An epithelial island containing several cysts filled with debris. Note columnar character of lining cells with transition to squamous type. (×270.)

CASE 3.—A white multipara, aged 53 years, was admitted to the clinic Dec. 5, 1927, with a diagnosis of obstructing carcinoma of the colon for which colostomy had been performed elsewhere six months previously. Her menstrual history had been normal, and her climacterium had occurred two years previously without incident. She was operated upon Dec. 22, 1927. Resection of the sigmoid with anastomosis was performed. Total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed for a solid tumor of the left ovary. The postoperative course was stormy, complicated by bronchopneumonia and terminal parotitis. Death occurred on the fifteenth postoperative day.

The specimen obtained at operation consisted of 10 cm. of sigmoid colon containing annular, ulcerated adenocarcinoma, Grade 2 (on the basis of 1 to 4), 4 by 4 by 2 cm. with several regional nodes involved by metastasis. The uterus, both tubes, and the right ovary were not remarkable. The left ovary was replaced by a solid, firm, grayish tumor measuring 4 by 3 by 2.5 cm., conforming to the general gross description outlined in Cases 1 and 2.

Microscopically, the picture was typical of Brenner tumor. An alveolar structure was entirely lacking, a fact which ruled out the possibility of the tumor being of a metastatic origin from the neoplasm of the sigmoid colon.

CASE 4.—A white multipara, aged 66 years, was admitted to the clinic, Aug. 10, 1933. She gave a history of bleeding for a period of four weeks which occurred twenty years following normal menopause. Examination gave negative results except for slight enlargement of the uterus.

On Aug. 17, 1933, abdominal hysterectomy and bilateral salpingo-oophorectomy were performed because of a report of adenocarcinoma in the endometrial scrapings on examination of a frozen section. A tumor measuring 2 cm. in diameter was found in the right ovary.

Microscopic examination of sections of the nodule, gave evidence of essentially the same picture as found in the specimen of Case 1, typical of Brenner tumor containing foci of calcification. Portions of this as well as portions of the left ovary contained the cortical and medullary tubular rests from which this tumor is supposed to take origin. No stages of transition, however, were obvious. Sections of the endometrium gave evidence of typical adenocarcinoma, Grade 2.

CASE 5.—A married, white woman, aged 61 years, registered at the clinic Dec. 24, 1927, complaining of vaginal "spotting" of six months' duration. Examination disclosed a fibromyomatous uterus with slight bloody discharge from the cervix. A mass in the left adnexal region was palpated. She was operated upon on Dec. 28, 1927, and total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed for uterine fibromyomas and for a left ovarian cyst. This patient was living and well when last heard from in 1935.

Pathologic examination disclosed a uterus with multiple intramural fibromyomas varying in size from 4 cm. to 1 cm. in diameter. At the fundus there was a degenerating adenomatous polyp measuring 4 by 3 by 2 cm. The endometrium was atrophic. Both tubes and the right ovary contained fibrotic changes. The left ovary was replaced by a multilocular pseudomucinous cyst with tiny intracystic papillomatous growths. One of these projections measured 1 cm. in diameter and grossly resembled fibroma. Microscopic sections of this nodule were typical of Brenner tumor.

CASE 6.—A married, white nullipara, aged 34 years, registered at the clinic July 21, 1918, complaining of irregular menses. For eighteen months her "periods" had occurred at intervals of four to seven weeks with profuse flow and considerable dysmenorrhea. Examination revealed multiple uterine fibromyomas and a mass in the left adnexal region. At operation on July 26, 1918, a large solid right ovarian tumor was found with many adhesions between it and neighboring structures. The uterus contained fibromyomas and was removed together with the ovarian tumor, both tubes, and the right ovary.

On pathologic examination, only a small portion of this tumor was preserved. Multiple sections, however, all contained evidence of Brenner tumor of the solid type.

CASE 7.—A married, white nullipara, aged 61 years, registered at the clinic on April 27, 1937, complaining of enlargement of the abdomen of six months' duration. Three years prior to registration, routine physical examination had revealed the presence of a pelvic tumor.

Examination confirmed the previous observation of a pelvic tumor now reaching the umbilicus. At operation on April 29, 1937, total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed for bilateral ovarian cysts. The patient was living and well nine months postoperatively.

Pathologic examination revealed a small, senile type of uterus. Both Fallopian tubes were chronically inflamed. The right ovary contained a simple follicular cyst 3 cm. in diameter. The left ovary was the seat of a multilocular pseudomucinous cyst 18 cm. in diameter with four solid intracystic nodules from 5 to 1 cm. in their greatest diameters. Examination of sections taken through these solid nodules all gave evidence typical of Brenner tumor.

CASE 8.—A single, white nullipara, aged 34 years, registered at the clinic Sept. 21, 1911, complaining of cramping pain of three weeks' duration in the lower abdomen. Menses had been regular.

On examination, a cystic tumor was palpated in the left adnexal region, for which operation was carried out on Sept. 28, 1911. Total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed for bilateral ovarian tumors and for uterine fibromyomas. This patient was living and well twenty-five years later.

On pathologic examination, the uterus was found to contain multiple fibromyomas. Both Fallopian tubes gave evidence of fibrous thickening. The right ovary was the seat of a typical multilocular, pseudomucinous cystadenoma, measuring 10 by 8 by 7 cm. The left ovary contained within its substance a fibrous nodule 2 cm. in diameter. Examination of microscopic sections of this nodule proved it to be Brenner tumor. Multiple sections through the wall of the right ovarian cyst failed to demonstrate any comparable picture.

CASE 9.—A married, white multipara, aged 59 years, registered at the clinic on Oct. 21, 1929, complaining of postmenopausal bleeding of nine months' duration. Pelvic examination disclosed an indurated, ulcerated cervix, manifestly carcinomatous. At operation on Oct. 29, 1929, a modified Wertheim type of hysterectomy was performed with removal of the adnexa. Postoperatively, a complete course of roentgen therapy was administered. When last heard from in 1935, this patient was living but had an inoperable, recurrent malignancy.

On pathologic examination, the uterine cervix was the site of squamous-cell epithelioma, Grade 3, measuring 4 by 4 by 3 cm. Both Fallopian tubes were mildly and chronically inflamed. The right ovary was atrophic. The left ovary was fibrotic and cystic but disclosed at its hilus an encapsulated fibrous nodule measuring 1 cm. in diameter. Microscopically, this nodule was typical Brenner tumor of the solid type.

CASE 10.—A married, white multipara, aged 65 years, sought medical advice at the clinic on April 7, 1934 for uterine prolapse of many years' duration. Examination revealed a relaxed perineum with uterine prolapse, Grade 3 (on a basis of 1 to 4).

At operation on April 9, 1934, Mayo vaginal hysterectomy with bilateral salpingo-oophorectomy and perineorrhaphy were performed. Convalescence was uneventful and the patient was living three and one-half years later.

On pathologic examination, the uterine cervix was considerably elongated and contained multiple cysts. Both tubes were chronically inflamed. The left ovary was atrophic. The right ovary, at its uterine pole, had a solid grayish tumor nodule, measuring 2 cm. in diameter. Microscopically, this nodule proved to be Brenner tumor of the solid type.

SUMMARY AND CONCLUSIONS

1. Ten cases of Brenner tumor are presented.

2. This type of tumor probably arises from ectopic ovarian hilar or cortical rests having no counterpart in the normal structural elements of the ovary and producing no physiologic alterations.

3. It occurs most often after the menopause.

4. It may occur either as a solid tumor or as a nodular projection in the wall of an ovarian cyst.

5. It grows slowly and nearly always is benign; prognosis is excellent following even local resection.

6. It may become partially calcified.

7. Brenner tumor of the ovary occurs much more frequently than is suspected. Microscopic sections in any series of so-called ovarian fibroma will bring to light many examples of this "new" and interesting neoplasm.

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THE USE OF TESTOSTERONE PROPIONATE IN THE TREATMENT OF DYSMENORRHEA

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IT APPEARS from recent reports that the immediate cause of pain in essential dysmenorrhea results from excessive spasmodic or tetanic contraction of the myometrium.[1-3] While this phenomenon is frequently associated with autonomic and psychogenic factors, it seems that for the most part such excessive contractions result from an endocrine imbalance. For example, it is known that initiation and maintenance of rhythmic uterine contractility is brought about by the follicular hormones, estrogens, which at the same time sensitize the myometrium to pituitrin.[4] The contractility and sensitization thus produced are diminished by the corpus luteum hormone, progesterone.[5] When estrogens are excessive or progesterone insufficient, exaggerated contraction results which the patient experiences as pain.

One of the earlier attempts to alleviate menstrual pain with an endocrine preparation, the luteinizing substance, antuitrin-S,[3] proved to be rather disappointing. The more direct use of progesterone[6, 7] met with more promising success.

Because testosterone, an androgenic product originally obtained from bull testis, but now synthetically produced from cholesterol, was found to be closely related chemically to progesterone[8] and because some of the androgens experimentally led to phenomena in many respects similar to progesterone,[9-12] it appeared advisable to study its effect upon the dysmenorrheic patient.

Twenty-six such patients were studied. The experiences encountered are best illustrated by the following case reports:

CASE 1.—L. S., white, single, twenty-eight years of age, well developed and nourished. Menstruation began at 14 years, recurred every twenty-four to thirty-five days and lasted four or five days. The flow was normal. Severe dysmenorrhea had been present from the onset of her first menstrual period. The pain which appeared with the flow was so severe that bed rest was required for twenty-four to forty-eight hours. Although she was then able to return to work, marked discomfort persisted throughout the period. Nausea, occasional vomiting, insomnia, and feelings of depression and anxiety accompanied the pain during the first one or two days.

Treatment consisted of two injections of testosterone propionate (Perandren-Ciba) in 5 mg. doses administered subcutaneously on the twentieth and twenty-third days of her menstrual cycle. Menses began on the twenty-fifth day and were practically free of all discomfort. She lost no time from work during this period, since she was free from digestive upsets, sleep disturbances, and the usual feelings of depression. During the next cycle the same treatment was repeated on the twenty-third and twenty-fifth days. Menses began on the twenty-sixth day again free from all discomfort.

During the third cycle it was decided to note the effect of the 10 mg. administered as a single dose. This was given on the twenty-fifth day and was followed the next day by menstruation which was accompanied by marked abdominal pain, nausea, and vomiting.

During the following cycle the hormone was again administered as two 5 mg. doses on the twenty-second and twenty-fifth days. Menses began on the twenty-seventh day with moderate discomfort during the first two hours. In the following four cycles the dose was increased to 15 mg., ten of which were administered on the twenty-second day, the remaining 5 mg. being given on the twenty-fifth day. This dosage has been sufficient to render her symptom-free.

CASE 2.—S. F., white, 13 years of age, studied in cooperation with Dr. M. H. Radman. Her complaint was painful menstruation for a duration of one year. Menses began at 10 years of age, recurred every thirty days and lasted six to seven days. For the first two years everything was normal. Following an attack of influenza and mumps at the age of twelve, there was a delay of menses for twelve days. Since then her periods have appeared regularly but have been accompanied by marked pain which confined her to her home for two to three days. Physical and gynecologic examinations revealed no pathologic findings.

Treatment consisted of 15 mg. of testosterone propionate (Perandren-Ciba) as 3 intramuscular injections of 5 mg. each on the day prior to the onset, when pain was first experienced, and on the first and second days of her flow. Complete relief from pain occurred after the second dose.

CASE 3.—E. R., white, 32 years of age, married six years, one pregnancy, one child living and well at five years, complained of painful menstruation and marked premenstrual tension manifested by swelling, tenseness and marked tenderness of the breasts for five days prior to menses and feelings of congestion and dragging pain in the lower abdomen for two to three days before onset of menses. In addition there was progressively increased emotional irritability during the three days preceding menstruation. Menses began at 15 years, recurred every twenty-five to thirty-five days and lasted seven or eight days. The flow was very profuse. Physical and gynecologic examinations were essentially negative, although her basal metabolic rate was lower than normal (minus 25 per cent). Thyroid medication which was sufficient to increase her basal metabolic rate to normal had no effect on the menstrual symptoms.

Testosterone propionate (Perandren-Ciba) was given intramuscularly in 5 mg. doses 3 times weekly for the last three weeks of her cycle. Menses occurred on the twenty-sixth day of that cycle. Although it was more profuse than previously the flow was smoother. Premenstrual tension and pain were completely relieved. Pelvic

congestion, however, was still present. The same therapy was followed for the next two cycles each of which lasted twenty-seven days. There was complete relief of all symptoms. While the duration of flow remained six days, the amount was reduced considerably.

The next six periods, during which time treatment was withheld, recurred at twenty-seven- to twenty-eight-day intervals, lasted six days, and were symptom-free except for a slight feeling of pelvic heaviness which occurred during the twenty-four hours prior to onset.

CASE 4.—D. E., white housewife, aged 31 years; one pregnancy, one child living at six years. Complained of severe menstrual pain which had become progressively worse during the last ten years. Physical and gynecologic examinations were essentially negative. Menses began at 14 years, recurred every twenty-one to twenty-three days and lasted four or five days. During the last ten years menses lasted seven days, with slight dribbling the first two days, full profuse flow for the next two or three days and diminution thereafter. Severe pain was present from the onset of full flow and remained for about forty-eight hours.

She was given 5 mg. of testosterone propionate intramuscularly three times weekly for the week before the next period. Menses occurred on the twenty-fifth day, were free from pain, and lasted five days. For the next three cycles she received 5 mg. of testosterone propionate 3 times weekly (except during menses). Menses occurred on the twenty-fifth day with complete absence of pain and considerable diminution in amount of flow. For the next two cycles, 5 mg. were given twice weekly (except during menses) with equally good results. For the next five months the patient was taken off treatment. Periods occur now at twenty-four- to twenty-six-day intervals, last five days, and are free from pain. However, staining for one day prior to the free flow has reappeared.

CASE 5.—J. L., aged twenty-four years, white, housewife, whose chief complaint was severe menstrual pain. Physical and gynecologic examinations were negative. Menses began at 15 years, recurred every twenty-one to twenty-five days, lasted six days and were accompanied by pain since her first period. The first two days of the period were marked by mere spotting. With the appearance of full flow, which was profuse, there was marked griping pain in the lower abdomen. Bed rest was required for relief.

She was given 5 mg. of testosterone propionate intramuscularly on the fifteenth, twenty-first, and twenty-fourth days of the cycle. Menses appeared on the twenty-eighth day and were free from pain. However, a slight feeling of pelvic congestion remained. The usual staining was also absent. This period lasted four days but was more profuse than usual. In an effort to diminish the amount of flow she was given 4 doses (5 mg. each) on the thirteenth, sixteenth, eighteenth, and twenty-second days of the next cycle. Menses appeared on the twenty-eighth day without pain and there was moderately reduced flow.

Treatment was discontinued because the patient expressed a desire to become pregnant. After two normal menstrual cycles entirely free from discomfort, she was successfully impregnated (Friedman Test).

CASE 6.—E. B., a 26-year-old housewife, who complained of irregular menses, profuse bleeding and marked pain at the time of menses. Physical and gynecologic examinations were negative. Menses began at 14 years, recurred every twenty-nine or thirty days and lasted four days. During the past one and one-half years, menses had been very irregular with profuse bleeding for four to five days (18 to 20 pads daily), which tapered off for one or two days, only to be followed by a copious flow during the next five to six days. Intermenstrual spotting has been present for the past six months. The pain which appeared twenty-four to forty-eight hours before the onset of the flow was accompanied by marked tenseness and tenderness of the breasts and severe frontal headaches. After its onset, the symptomatology remained for two days, was gradually alleviated during the next four or five days and reappeared with full vigor with the recurrence of profuse bleeding.

An endometrial biopsy taken the day before the calculated date of onset disclosed a normal endometrium characteristic of the follicular phase of the cycle. She was given testosterone propionate (Perandren-Ciba) in 5 mg. doses intramuscularly every other day for 4 doses. Menses set in on the ninth day of therapy; i.e., the flow was apparently delayed for eight or nine days.

The flow during this period was profuse for the first two days but only 8 pads were required instead of the usual 18. Pain was slight. Because of returning pain on the seventh day of this period she was given 10 mg. of the hormone intramuscularly. This was followed by a marked increase in flow that evening which completely subsided by the next morning.

Since then, without further treatment, she has remained practically symptom-free, menses recurred at twenty-eight- to thirty-day intervals, lasting four to six days, being normal in amount. An endometrial biopsy taken two months after treatment on the twenty-third day of the cycle disclosed a secretory picture.

CASE 7.—F. G., white, married but separated; had had 2 pregnancies resulting in 2 living children who are normal, 3 and 6 years of age, respectively. Her complaint was severe menstrual pain and profuse bleeding from the onset of her first period. Menses began at 12 years of age, recurred every twenty-eight to thirty-two days and lasted five or six days. During the first day of her period the flow was scant and pain was crampy and slight in nature. During the second and third days the pain became worse until it was so excruciating that she had to retire to bed. In addition, the flow became very profuse, saturating at least 12 pads daily. Breast pain appeared twenty-four hours prior to the onset of the flow and lasted for about forty-eight hours.

On the second day of her menstrual period just as severe pain was developing she was given her first injection of 5 mg. of testosterone propionate intramuscularly. Within two hours her pain had completely subsided and the relief lasted for the remainder of the period. The amount of flow, however, was slightly but definitely increased. During this same cycle, 5 mg. doses were repeated on the twenty-fourth and twenty-eighth days. Menses appeared on the twenty-ninth day, free from pain. The usual premenstrual breast tension was also absent. Bleeding was as profuse as usual. On the twenty-third and twenty-sixth days of the next cycle the same therapy was repeated. Menses began on the twenty-eighth day with but slight backache and cramps for the first two hours after which she remained asymptomatic. The flow was as usual.

During the third cycle, injections (5 mg.) were given on the twenty-first and twenty-fifth days. Menses set in on the thirtieth day with no pain. The amount of flow was diminished, however, being estimated by the patient as being less than half the usual amount (3 or 4 pads daily). No therapy has been given for the last two periods. The patient has menstruated on the twenty-ninth and thirtieth days, respectively, and aside from slight cramps and mild backache for several hours has remained comfortable. Her flow has remained moderate.

CASE 8.—M. G., white, single, 20 years of age, laboratory technician whose complaint was "dysmenorrhea and profuse menstrual bleeding." While the patient was of slender build, physical and gynecologic examinations were otherwise normal. Menses which began at 11 years of age had always been irregular, recurring every twenty-one to thirty-five days. During the past three years they have been recurring at twenty-one- to twenty-five-day intervals, lasting six or eight days.

The flow was always profuse especially during the first four days when 12 to 15 napkins were saturated daily. Her present complaint dates from her first menstrual period. Pain begins twenty-four to forty-eight hours before the discharge makes its appearance and becomes so severe that at the onset of the flow she has to take to bed where she remains for thirty-six to forty-eight hours. Marked nausea, occasional vomiting, cold sweats and dizziness are present at the height of pain. The last three to five days of flow are accompanied by a continuous ache in the lower abdomen. Once in her entire menstrual history she has been free from pain. This occurred about three years ago.

Treatment was begun on the first day of her menstrual flow at which time she was in agony. Ten milligrams of testosterone propionate were administered, 5 mg. intra-

muscularly and 5 mg. subcutaneously. Relief of pain began in two hours and within twenty-four hours was complete. Her flow, however, was markedly increased in amount that evening but by the next day had decreased to such an extent that she required but 6 pads. During the next two days, only 2 or 3 pads were utilized. In order to completely stop bleeding 30 mg. of the hormone were administered in 3 daily 10 mg. doses intramuscularly during the third, fourth, and fifth days, respectively. While the amount of daily bleeding was diminished the period was extended to eleven days with mere spotting during the last four days. Five-milligram subcutaneous doses were administered on the thirteenth, sixteenth, nineteenth, and twenty-first days of this cycle. Menses began on the twenty-first day and were free from all discomfort and pain. The flow was characterized by mere staining for forty-eight hours, was normal during the third day, then tapered off, to cease on the fifth day.

For the past two months she has received 5 mg. subcutaneously on the nineteenth or twentieth day of the cycle. Menses during these two cycles have occurred on the twenty-sixth and twenty-second days, respectively, with normal flow for a period of five days, entirely free from discomfort.

CASE 9.—H. S., white, single, 31 years of age. Her chief complaint was severe menstrual pain accompanied by nausea and marked premenstrual occipital headaches.

General physical examination showed no gross abnormalities but gynecologic study by Dr. M. H. Radman disclosed a palpable right kidney extending down to mid-abdomen. The cervix was small but the uterus was normal in size; although it was retroflexed in midposition, the uterus was freely movable. The adnexa were negative. Menses began at the age of 11, recurred at twenty-one to twenty-five days, lasting six or seven days. Her present illness dates from her first menstrual period. Various sedatives and anterior pituitary-like hormone were administered for several months without relief. Testosterone propionate was then substituted. Ten milligrams were given on the twenty-fourth day and 5 mg. on the twenty-sixth day of her cycle. Menses occurred on the thirty-second day with a mild discomforting pain in the abdomen which lasted about ten hours the first day. The headache appeared in mild form three hours before the flow which lasted but three days. During the next cycle (twenty-four days) no therapy was given and all her symptoms returned. During the next 4 cycles, however, testosterone propionate administered in various dosages and methods has failed to relieve her symptoms.

CASE 10.—L. G., white, single, 36 years of age, complained of very severe pain associated with menstruation which was accompanied by nausea during the first twenty-four hours of flow and marked premenstrual breast pain a day before the onset. Menses began at 14 years; recurred at twenty-eight- to thirty-day intervals and lasted three days. The flow has always been scant.

Physical examination disclosed an obesity of the pituitary type. The basal metabolic rate was found to be minus 18 per cent. In addition, there was a marked anxiety because of her precarious economic situation. Treatment by means of dietary restriction, pituitary preparation (Pituitrin-O and anterior pituitary extract, Squibb) and sufficient thyroid substance which led to loss of weight and an increased metabolic rate (plus 10 per cent) failed to influence the dysmenorrhea. While psychotherapy involving a discussion of her conflicts led to a diminution of her anxiety and feelings of insecurity, dysmenorrhea continued.

A day before her expected period she was given 10 mg. of testosterone propionate (Perandren-Ciba) intramuscularly. Menses appeared the next day with the usual nausea and pain but the breast pain was absent.

On the twentieth day of her second cycle she received 5 mg. but did not appear for a scheduled injection on the twenty-fifth day. Menses occurred on the twenty-eighth and the pain was worse and lasted longer than usual. The flow also was more marked.

During the third cycle she received 10 mg. subcutaneously on the twentieth and twenty-fifth days. Menses occurred on the twenty-sixth day with freedom from pain except for very mild discomfort. The flow was moderate. Since then, over a period

of five cycles, testosterone propionate given in progressively larger doses during the week before menses (and during one month, throughout the cycle) has failed to relieve the symptoms. During all this time, the patient has consistently refused to undergo a gynecologic examination.

Sixteen additional cases not reported in detail showed features which were not strikingly different from those above so far as the method of treatment is concerned. The results in all the twenty-six cases, therefort, are best summarized as follows:

1. Sixteen patients obtained complete relief. Of these, 15 had a functional disorder and 1 had a chronic salpingitis.

2. Four patients were partially relieved. Of these, 2 had infantile uteri and 2 had retroverted uteri.

3. Four cases failed to respond to the therapy. Of these, 2 were functional, 1 had an infantile uterus, and 1 had a chronic salpingitis.

4. Two patients experienced an aggravation of symptoms. Of these, 1 was functional (?), and 1 had an infantile uterus. One of the patients (L. G.) who was made worse during one of her periods refused to submit to gynecologic examination and has been classed as functional (?).

DISCUSSION

From the foregoing it will be noted that the greatest relief was obtained in patients with "essential" dysmenorrhea. Most observers now believe that hormonal imbalance is the major etiologic factor in these cases. The treatment of this disorder with proper endocrine preparations is, therefore, quite logical.

The use of testosterone propionate in this condition, as explained previously, was based on its progesterone-like action. It is well established that functional dysmenorrhea is frequently associated with high estrogen concentration in blood and urine.[13] This is particularly true just prior to menstruation when, in addition, there is a rise of pituitary gonadotropic substance.[14]

Because testosterone propionate depresses pituitary gonadotropic secretion[15] and inhibits ovulation[16] it leads to the suppression of estrogen formation. In addition, by favoring luteinization and maintaining the corpus luteum,[17] it increases the progesterone-like effect. This leads to myometrial relaxation, myometrial growth through its trophic effect, and progestational response in the endometrium.

The most striking effect clinically, however, is the relief of menstrual pain. That this results from uterine relaxation is indicated by preliminary studies on "afterpains" which were also relieved by this hormone.

The relief of premenstrual tension and profuse bleeding is also explainable on the progesterone-like effect of the substance used.

CONCLUSION

Testosterone propionate has been found to relieve most cases of essential dysmenorrhea. It has not been as helpful in organic or anatomically determined dysmenorrhea. This substance will frequently relieve

and in some cases cure the varied aspects of premenstrual tension. It has been found to be a valuable asset in functional uterine bleeding.

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BILATERAL INTRALIGAMENTOUS LIPOMAS OF THE BROAD LIGAMENT

Report of Two Cases

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USING the literature alone as an index, intraligamentous lipoma is a rare tumor, only 14 examples having been recorded to date and of these two were not regarded as true neoplasms. On the other hand the fact that Watkins[1] has observed several broad ligament lipomas in his operative gynecologic cases during the past several years and has not reported them, lends support to the well known fact that some of the apparent rarities in human pathology are more common than is generally supposed, solely because they are not put on record.

The condition was first mentioned by Pollock[2] in 1852. He encountered one instance of simple lipoma in the substance of the broad ligament in a series of 538 necropsies. In 1919 Lockyer[3] discovered another at an operation for dermoid cyst of an ovary. The lipoma, typical in form, lay in the broad ligament in contact with the dermoid, entirely free from the cyst or its contents although lipoid matter did extend along the external wall of the cyst. Lockyer reviewed the literature and found 9 other cases, 7 of which he regarded as true lipomas. Two were rejected because of their association with dermoids. In one the cyst had ruptured, allowing dissection of the fatty contents between the layers of the broad ligament; the other showed an infiltration of fatty material into the broad ligament and about the dermoid. In 1926 Rawls[4] published his account of an operation on a negress for multiple fibromyoma and ovarian cyst in whom the supposed cyst proved to be a large lipoma in the left broad ligament. In a survey of the literature Rawls mentions Lockyer's case and adds those of Pollock and Klein which appeared in 1909. A careful check of the literature from 1926 to March, 1938, has disclosed only one additional instance, that of Kanter,[5] in 1935. The clinical history in this case justified the diagnosis of incomplete abortion. Vaginal examination disclosed a very small uterus which was displaced laterally; on the left side was a rather soft tumor

that reached the crest of the ilium. The preoperative diagnosis was hydrosalpinx. The uterus and tubes proved to be normal, but one broad ligament contained a more or less lobulated lipoma about 20 cm. in diameter which shelled out easily from the folds of the ligament excepting at the lower pole where it was intimately associated with the deep pelvic and femoral vessels from which the blood supply was derived.

Lockyer's summarization reveals only one example of bilateral lipoma of the broad ligaments, that of Emrys-Roberts, who described a small tumor of this type in each ligament in conjunction with an ovarian fibroma and multiple uterine fibroids.

According to Rawls the lipomas hitherto observed have varied from diameters of a few centimeters to "very large size." Middelschulte[6] removed one weighing thirty-three pounds and measuring 88 by 90 cm. The age of the patients has ranged from 31 to 64 years. In three of the reported cases and in one of ours, intraligamentous lipoma constituted the sole lesion; associated pathology was present in five, while the remainder are silent on this point. In most instances the symptoms have led to the preoperative diagnosis of ovarian cyst.

The rarity of broad ligament lipomas is believed to be due to the normal lack of fat in this location. While several possible etiologic factors have been proposed none are at all convincing. Metaplasia from connective tissue is a possible factor.

CASE REPORTS

1. Mrs. R. W. W.,* aged 55 years, complained chiefly of pain in both lower quadrants; this symptom had been present for approximately a year, was intermittent in type and of increasing severity, lasting two to three days. For the past few months she had been conscious of a swelling in the left side of the abdomen. In addition there was some frequency of urination and nocturia (2-3 times). Over a five-year period, but subsiding two years ago, vaginal bleeding occurred every three months. Menstruation began at the age of twelve, was of twenty-eight day cycles, lasted two to three days and was never excessive. Four pregnancies resulted in three living children and one miscarriage.

Pertinent Physical Findings: The abdomen was too obese for satisfactory examination by palpation. There was a slight tenderness immediately above the left inguinal region. On bimanual palpation the uterus seemed to be normal in size and position; a soft, somewhat boggy mass was felt in the left adnexa and a smaller one of similar consistency was made out on the right side. The preoperative diagnosis was left intraligamentous parovarian cyst. The laboratory reports on blood, urine, and serology were essentially normal and are therefore omitted in order to conserve space.

On opening the abdomen the enlarged and widened broad ligaments of the uterus were seen to encase quite large masses of yellow tissue, the larger swelling being on the left side. The anterior reflection of one broad ligament and the posterior aspect of the other were incised parallel to the round ligaments and oviducts. The fatty tumors were then easily removed by blunt dissection. There proved to be four separate and distinct masses, two on either side. The patient made an uneventful recovery.

Pathologic Description: Four quite discrete tumors having a combined weight of 270 gm. were present. Externally two appeared quite smooth and regular in contour, while the others presented somewhat serrated and lobulated outer surfaces. The dimensions of the several specimens were 6.5 by 4 by 3 cm., 8 by 6 by 3 cm., 11 by 10 by 3 cm., and 9 by 6 by 4 cm. Multiple sections through each growth revealed all to consist very largely of quite pale yellow adipose tissue with only a slight admixture of fine fibrous trabeculae. Quite a number of small blood vessels could be made out.

Microsections from each tumor disclosed mostly fat cells of adult type, variable in size and shape and possessing cell membranes that quite often seemed to be thicker than is the case for normal adipose tissue. None were immature and lipoblasts proved to be altogether lacking, thus excluding liposarcoma.

Pathologic Diagnosis: Bilateral intraligamentous lipomas.

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*We are indebted to Drs. W. B. Holden and L. T. Nelson for permission to report this case.

2. Mrs. C. A. DeW., 70 years of age, sought attention for profuse vaginal bleeding of only three days' duration, accompanied by slight lower abdominal discomfort. Except for the common signs of senility and poor body nourishment, the physical examination was negative. A diagnostic curettage yielded friable material which in immediate frozen sections was interpreted as an anaplastic adenocarcinoma of the corpus uteri. Upon opening the peritoneal cavity Drs. Holden and Rippey observed no evidence of extension of the neoplasm to the surface of the uterus or beyond it and accordingly performed a panhysterectomy.

Pathologic Description: The entire uterus, either ovary and both tubes had an aggregate weight of 100 gm. Obliterating the left cornu and spreading out over the anterosuperior aspect of the cavum uteri was a crateriform mass, 2.5 cm. in maximum diameter, which had destroyed the myometrium to within 1 cm. of the external surface; the endometrium elsewhere was thin, obviously atrophied and noncarcinomatous. The ovaries were small and atrophic; the oviducts were unchanged.

The mesosalpinx division of the left broad ligament was present posteriorly and in part anteriorly as well but all of the remainder of the ligament had been divided at the uterine end. Viewed anteriorly one could see on this side, adjoining the uterus and between the tube and ovary, a mass of ordinary appearing yellow fat, measuring 3 cm. in length, 2 cm. in breadth and 1 cm. in thickness anteroposteriorly.

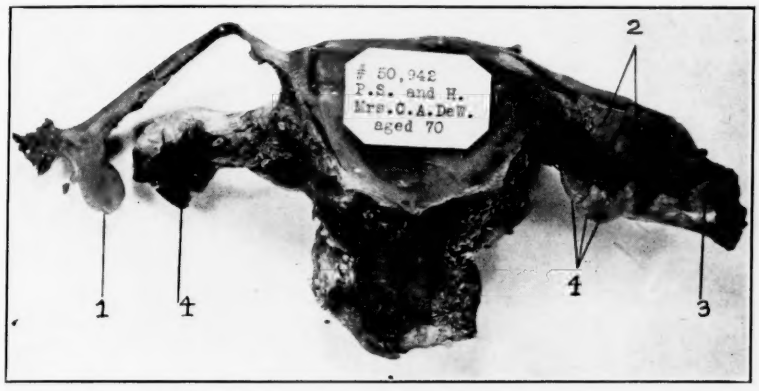

Fig. 1.—Anterior view of uterus and adnexa from Case 2. *1*, Lipoma near fimbria of right tube; *2* and *3*, two of the four lipomas in the left mesosalpinx; *4*, ovaries.

Continuous with this, still lying between the folds of the mesosalpinx, were two additional fatty lobules, covering an area 2.2 by 1.5 by 0.5 cm. Between the epoöphoron and the tubal ampulla, against which it abutted, was another discretely outlined body of fat 1.5 by 1.3 by 0.5 cm. whose lateral border came within 1 cm. of the tubal fimbria. From the opposite side of the mesosalpinx only the two more laterally placed masses could be discerned beneath the peritoneal covering. None of the fatty masses compressed the tube or extended into the hilum of the ovary.

On the right side the only portion of broad ligament present was a triangular segment, 2.5 cm. in breadth, situated inferior to the ovarian ligament posteriorly. Attached to the inferior and denuded aspect of the right tube, 5 mm. mesial to the fimbria and obviously having been interposed between the layers of the missing mesosalpinx was an ovoid yellow blob of fat, measuring 1.5 by 1.5 by 0.6 cm. and containing a goodly number of small and engorged blood vessels running parallel with one another and at a right angle with the tube. Near the tubal attachment the otherwise smooth and regular surface was interrupted by a small hornlike tab of fat. Just inferior to the hilum of the right ovary, but not extending into it, was another accumulation of fat, crescentic in outline and measuring 1.5 by 0.5 by 0.5 cm.

Microscopic sections from the various fatty masses displayed an abundance of fully differentiated fat cells, varying from normal only in being somewhat larger in diameter and apparently thicker walled.

Pathologic Diagnosis: Adenocarcinoma of corpus uteri (Grade III); senile atrophy of uterus and adnexa; bilateral small intraligamentous lipomas, limited to mesosalpinx portion of these structures.

COMMENT

Among the uncommon tumors of the female generative organs one of the least frequent appears to be intraligamentous lipoma. A plausible explanation for this is the normal absence of adipose tissue between the folds of the broad ligaments. False lipomatous growths have been known to occur in conjunction with dermoid cysts of the ovaries. It is also possible for a retroperitoneal lipoma originating in the vicinity of the ligaments to present itself between the leaves of the structure and thus appear to have originated here. Of the twelve acceptable examples hitherto recorded, only one in addition to the two herein described has proved to be bilateral.

When sufficiently bulky, growths of this type are fully capable of manifesting themselves clinically as exemplified in Case 1. This tumor and some of those already in the literature simulated an ovarian or parovarian cyst.

In the second instance, the small size of the lipomas both individually and collectively readily explains their clinical silence. This case is included only on account of the rarity of broad ligament lipomas, the apparently unique localization in the mesosalpinx and the bilateral distribution of the masses. We have been unable to find descriptions of lipomas limited to the mesosalpinx among the previously recorded examples. Sampoerno's[7] case differs from ours in that the lipoma lay beneath the tubal serosa, opposite the mesosalpinx, where it produced marked compression of the lumen. It might be argued that the fatty masses we have described are not lipomas. However, the occurrence in a situation normally devoid of any appreciable amount of adipose tissue, the formation of discrete masses and the presence of such nodules in a woman with little body fat anywhere, make it reasonable to assume that the accumulations are really lipomas.

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SUPERFETATION IN UTERUS DIDELPHYS

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Mrs. B., 22 years of age, a young, robust, well-formed female, weighing 120 pounds and 5 feet 4 inches tall, first seen March 2, 1937.

First menstrual period at 10½ years of age, always irregular, considerable bleeding, 6 to 7 days. Last period on Nov. 1, 1936. Fundus about one finger about the symphysis. Vaginal examination disclosed two distinct and separate introiti divided by a thick septum extending from immediately beneath the urethral orifice to the frenulum labiorum and reaching to the pouch of Douglas and apparently fusing with it, thus forming two complete and separate compartments, each one presenting a distinct and normal cervix.

Bimanual palpation did not disclose any other unusual findings. Neither the patient nor the husband were aware of any abnormality. She never complained of any discomfort due to her pregnancy, except for an occasional slight pyrosis. At the end of the seventh month an x-ray plate was taken. The skeleton of an apparently normal fetus was found on the right side, vertex presentation, measuring twelve inches from vertex to coccyx. There was nothing indicated on the left side to the presence of another pregnancy.

On July 12, 1937, I was called to see the patient at her home. At that time she complained of slight pain in the back and some "spotting." Rectal examination showed no dilatation of the cervix. Patient was given half a grain of codeine twice daily and ordered to stay in bed.

On July 13, at 9 P.M. the patient complained of severe bleeding and of passing "large pieces of something." Upon examination it was found that there was a moderate amount of bleeding and that large pieces of placental tissue were protruding from the vagina, besides a considerable amount of placental tissue passed before my arrival. I could not locate the fetal heart. The patient was taken to the hospital and a vaginal examination done. The cervix on the left side was dilated about 1½ to 2 fingerbreadths. Pieces of placenta and many large blood clots were found in the vagina. The cervix on the right side was completely closed. The patient insisted that she could feel the baby on several occasions during the examination, but no heart sounds were audible. At this point an immediate cesarean section was decided upon with the idea in mind that the fetus was still viable.

Fig. 1.—Lipiodol injection three months after operation.

A lower midabdominal incision was made. A gravid uterus containing an eight to nine months' pregnancy with the placenta attached low on the anterior wall and partly obliterating the internal os was found. The placenta was perforated and an almost full-term fetus extracted.

To the left of the emptied uterus another, about the size of a two months' pregnancy, with normal tube and ovary, was found lying in the left half of the pelvic cavity. A pronounced plica umbilicalis media extended downward from the umbilicus and acted as a curtain between the two uteri.

About twenty hours after the operation, the vulval pad was examined. A fetus measuring 1¾ inches (4.4 cm.) in length from crown to coccyx was found. It seemed that the embryo had been dead not over seventy-two hours, as it was very well preserved, except for the lack of several strips of skin over various parts of the body. The patient's convalescence in the hospital was uneventful and she left on the twelfth day after the operation with a 7-pound living male child, completely recovered.

The foregoing evidently was a case of true superfetation.

451 KINGSTON AVENUE

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

MATERNAL AND CHILD HEALTH SERVICES

THE extent and distribution of Federal grants under the Social Security Act for the fiscal year ending June 30, 1938, are presented in a report made by Dr. Edwin F. Daily, Director of the Division of Maternal and Child Health of the Children's Bureau. This is based on reports received from State health agencies, which are preliminary and incomplete and represent primarily activities of various health departments but include services provided by other public and private agencies. The collected information discloses, however, the extent of governmental activities in this field.

Medical Services.—

Conferences for maternity service, total patients' visits			281,210
Ante-partum service		263,165	
Post-partum medical examination		18,045	
Conferences for child hygiene service, total patients' visits			939,031
Infants		481,358	
Preschool children		457,673	
Health examinations of school children			1,994,342

Public Health Nursing Service.—

Total office and home visits			6,222,723
Maternity service, total office and home visits		1,061,388	
Ante partum	597,043		
Delivery	14,655		
Post partum	449,690		
Child hygiene service, total office and home visits			5,161,335
Infants	1,279,420		
Preschool children	1,072,917		
School children	2,808,998		

Immunizations.—

Diphtheria, number of persons immunized	995,434
Smallpox, number of persons immunized	1,619,190

Dental Inspections.—

Inspection by dentists or dental hygienists, total			1,525,025
Preschool children		127,545	
School children		1,397,480	

Midwife Supervision.—

Midwives under planned instruction, as of June 30, 1938	11,127
Number of midwife meetings	11,294
Attendance at midwife meetings	68,820

AMOUNTS BUDGETED FROM MATCHING AND FEDERAL FUNDS IN STATE MATERNAL AND CHILD HEALTH BUDGETS FOR THE FISCAL YEAR ENDING JUNE 30, 1939

For Professional Personnel and Services, and Postgraduate Education			
Grand Total	$6,102,396.55	100%	
Professional Personnel and Services.—			
Total	*5,859,058.41*	96%	
Salaries and travel for 456 state and local staff physicians	1,034,489.76	17%	
Fees to local practicing physicians for conferences, school medical examinations, and home delivery service and consultation	316,014.14	5%	
Salaries and travel for 67 dentists, 52 dental hygienists, and 2 dental health educators on state and local staffs	305,341.56	5%	96%
Fees to local dentists	88,249.04	2%	
Salaries and travel for 43 nutritionists	126,245.15	2%	
Salaries and travel for 34 health educators	101,081.96	2%	
Salaries and travel for 2,822 public health nurses	3,866,382.29	63%	
Fees to local practicing nurses for home delivery service	21,254.51	*	
Postgraduate Education.—			
Total	*243,338.14*	4%	
Medical	146,836.14	3%	
Nursing	83,951.99	1%	
Dental	8,765.00	*	4%
Health education	3,115.01	*	
Nutrition	670.00	*	

*Less than 1 per cent.

Society Transactions

AMERICAN ASSOCIATION OF OBSTETRICIANS, GYNECOLOGISTS AND ABDOMINAL SURGEONS

FIFTY-FIRST ANNUAL MEETING

White Sulphur Springs, W. Va., September 22, 23, and 24, 1938

The following papers were presented:

Presidential Address—Obstetrics and Gynecology as a United Specialty. Dr. Paul Titus, Pittsburgh, Pa. (For original article, see page 545.)

The Etiology of Occiput Presentations. Dr. L. A. Calkins, Kansas City, Mo. (For original article, see page 618.)

Sterility Studies. Dr. Otto S. Krebs, St. Louis, Mo.

Recent Developments in Diagnosis and Treatment of Hydatidiform Mole and Chorioepithelioma. Dr. Albert Mathieu, Portland, Ore. (For original article, see page 654.)

Clinical Syndromes Referable to Failure of Ovulation. Dr. Emil Novak, Baltimore, Md. (For original article, see page 605.)

Inversion of the Uterus With Repeated Hemorrhages and Replacement by the Use of the Aveling Repositor. Dr. J. K. Quigley, Rochester, N. Y. (For original article, see page 696.)

The Biologic Significance of the Fetal Membranes. (Joseph Price Oration.) Dr. Charles Burger, Budapest, Hungary. (For original article, see page 572.)

Behavior of the Basal Metabolism in the Course of Developing Toxemia of Pregnancy: Correlation With Cholesterol, Placental Infarcts and Retinal Examination. Drs. D. Colvin and R. A. Bartholomew, Atlanta, Ga. (by invitation). (For original article, see page 584.)

Management of Breech Delivery in Primiparas. Dr. Thomas R. Goethals, Boston, Mass. (by invitation). (For original article, see page 663.)

Maternal and Fetal Expectations With Multiple Pregnancy. Dr. John C. Hirst, Philadelphia, Pa. (by invitation). (For original article, see page 634.)

The Relation of Ureteral Pain to Menstruation. Dr. Nathan P. Sears, Syracuse, N. Y. (For original article, see page 685.)

Puerperal Sepsis. Dr. Carl H. Davis, Wilmington, Del.

The Increased Incidence of Fetal Abnormalities in Cases of Placenta Previa. Dr. J. P. Greenhill, Chicago, Ill. (For original article, see page 624.)

Benign Tumors of the Cervical Stump Following Supravaginal Hysterectomy. Dr. Mortimer N. Hyams, New York, N. Y. (For original article, see page 690.)

The Pitfalls of Podalic Version and Extraction. Dr. Milton G. Potter, Buffalo, N. Y. (For original article, see page 675.)

Prevention and Treatment of Postoperative Thrombophlebitis. Drs. N. W. Barker and V. S. Counseller, Rochester, Minn. (For original article, see page 644.)

Studies on the Endometrium in Association With the Normal Menstrual Cycle, With Ovarian Dysfunctions and Cancer of the Uterus. Dr. Wallace E. Herrell, Rochester, Minn. (For original article, see page 559.)

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Extrauterine Pregnancy

Pütz, T.: Extrauterine Pregnancy, Monatschr. f. Geburtsh. u. Gynäk. **104:** 57, 1936.

The author studied a series of 300 cases of ectopic pregnancy. He believes the chief cause is to be found in inflammatory changes of the genitalia. Helpful procedures in making a diagnosis are as follows: (1) The white blood count and the sedimentation test, (2) bimanual examination under evipal, (3) puncture of the cul-de-sac of Douglas, (4) exploratory curettement of the uterus, (5) the Aschheim-Zondek pregnancy test, and (6) exploratory laparotomy.

In the author's clinic, every patient with an ectopic gestation is operated upon as soon as the diagnosis is made. The operation is usually limited to removal of the involved tube. The death rate in this series was 2 per cent.

J. P. GREENHILL

Nixon, W. C. W.: Aids in the Diagnosis and Treatment of Ectopic Gestation, Brit. M. J. **2:** 579, 1937.

In the diagnosis of ectopic gestation one must evaluate carefully the history, symptoms, and signs. The history of recurrent attacks of low abdominal pain, accompanied by periodic or continuous uterine bleeding, is very significant. Pulsation in one or other fornix is always present and confirms the diagnosis. It is felt best at the junction of the vagina and cervix by gentle palpation. Puncture of the posterior fornix is a useful aid in diagnosis, if doubt exists, in the acute tubal rupture type.

Treatment is operative in all cases of hematocele, no matter how small it is and irrespective of how ill or well the patient appears to be. Drainage should be avoided. The author favors autotransfusion in the acute cases, where there is free intraperitoneal bleeding and absence of infection. The abdominal route should be employed in all cases in the absence of infection. Where, however, an hematocele has become infected and a pelvic abscess is present, drainage through the posterior vaginal fornix is the method of choice. Seven cases of diverse type are reported.

F. L. ADAIR AND S. A. PEARL

Hope, Robert B.: The Differential Diagnosis of Ectopic Gestation by Peritoneoscopy, Surg. Gynec. Obst. **64:** 229, 1937.

The diagnosis of ectopic gestation is not always simple. In the differential diagnosis, peritoneoscopy is a valuable adjunct. It is a safe procedure and in cases of actual intrauterine pregnancy, an abortion is far less likely to occur after it than after exploratory laparotomy.

In questionable cases peritoneoscopy can be used to determine by direct eye-control whether surgery or expectant treatment is indicated. Ten case histories are presented to show the procedure in this field.

WILLIAM C. HENSKE

Siddall, R. S., and Jarvis, Charles: Uterine Curettage as an Aid in the Diagnosis of Ectopic Pregnancy, Surg. Gynec. Obst. **65:** 820, 1937.

In view of the frequent difficulties met with in the recognition of ectopic pregnancy, a study was made of uterine curettage as a diagnostic aid. The pro-

cedure is apparently not unduly dangerous, and the finding of intact decidua without chorionic villi is strong presumptive evidence of extrauterine pregnancy. In 38 cases of proved ectopic pregnancy with available specimens of endometrium, intact decidua alone was present in all cases with abnormal bleeding of ten days or less and in a considerable proportion of those with more prolonged bleeding. The absence of decidual reaction is not reliable evidence against ectopic pregnancy. However, if chorionic villi are also absent, the findings may be of value in ruling out uterine abortion as a cause of the bleeding. Three of four somewhat comparable series found in the literature confirmed the results in large part. Two illustrative case reports are given.

WILLIAM C. HENSKE

Bortini, Ennio: Confirmation of the Various Forms of Ectopic Pregnancy by Hysterosalpingography, Ann. di ostet. e ginec. **16**: 1247, 1937.

The author points out the characteristic x-ray signs of the various forms of ectopic pregnancy. This method offers the assurance of a correct diagnosis not only of ectopic pregnancy but also the differentiation of its various forms and their complications.

He emphasizes the necessity of numerous x-ray plates and a long fluoroscopic examination.

He further recommends that the procedure be limited to the doubtful cases, to maintain an aseptic techniue and to be prepared for immediate intervention.

AUGUST F. DARO

Massé and Laporte: High Pain and Leucocytosis in Ruptured Ectopic Pregnancy, Bull. Soc. d'obst. et de gynéc. **26**: 282, 1937.

The usual signs of ruptured tubal pregnancy are not always sufficient to permit a diagnosis of this condition. Certain signs, however, may be of help. Among these are pain high up and hyperleucocytosis. This pain appears a few hours after rupture but not when the rupture actually occurs and is due to peritoneal inundation of blood. It usually continues for twenty-four to forty-eight hours after operation but may persist for many days. It is always high up in the thoracic region, always unilateral, and always on the right side. However, this sign is not pathognomonic of ruptured ectopic pregnancy, because it may exist in many other conditions, medical as well as surgical. It is not always present but when it occurs it has a prognostic value because it indicates severe hemorrhage.

An increase in the number of white blood cells is also of prognostic importance because it denotes acute hemorrhage. It occurs early and is an indication for immediate operation. This sign likewise is not pathognomonic of a ruptured tubal pregnancy.

J. P. GREENHILL

Ehrhardt and Kramann: Clinical and Hormonal Errors in Diagnosing Ectopic Pregnancies Because of Corpus Luteum Cysts, Zentralbl. f. Gynäk. **60**: 2642, 1936.

The writers report the case of a woman who, after missing a menstrual period, developed sudden pain in the lower abdomen and collapsed. Examination revealed an enlarged uterus and a cystic mass to the right of the uterus. An Aschheim-Zondek test was positive. A diagnosis of ectopic pregnancy was made and a laparotomy performed. However, no pregnancy was found but a cyst of the right ovary. It was removed and proved to be a corpus luteum cyst. Another Aschheim-Zondek test was made the day after operation, and again it was positive. Hence, in this case the hormone pregnancy test was fallacious.

A similar case was recently reported by Kaiser. The Aschheim-Zondek test as a specific test of pregnancy has limitations. Cases of persistent corpus luteum may give a positive reaction. On the other hand, ectopic pregnancy may be present also when the test is negative.

J. P. GREENHILL

Banister, J. Bright: Simultaneous Intra- and Extra-Uterine Pregnancy, Proc. Royal Soc. Medic. **30:** 562, 1937.

Patient was a primigravida, in fourth month, without any complaint, presenting herself for antenatal care. A tumor on the left of pregnant uterus was diagnosed as ovarian cyst complicating pregnancy. At laparotomy the ovoid tumor on the left was found to be the size of a twelve weeks pregnant uterus and to represent an ectopic pregnancy in an accessory horn. Mass was excised but the intrauterine pregnancy continued undisturbed to term with delivery of a live infant.

HUGO EHRENFEST

McIlrath, Muriel B.: Bilateral Tubal Pregnancy, Brit. M. J. **1:** 1065, 1937.

This is a case of bilateral tubal pregnancy in a gravida ii with a definite history of several attacks of salpingitis. The latter condition may be an etiologic factor in the incidence of tubal pregnancy. The operative findings are described, and methods of treatment discussed. The author favors double salpingectomy with conservation of the ovaries or portions of the ovaries, and the uterus.

F. L. ADAIR AND S. A. PEARL

Martz, Harry: Repeated Ectopic Pregnancy Simulating Intestinal Obstruction, Am. J. Surg. **40:** 483, 1938.

A case of repeated ruptured tubal pregnancy with secondary abdominal implantation which simulated a case of low ileal obstruction is presented. The incidence of repeated ectopic gestations is discussed, and the importance of examination of the opposite tube is emphasized in determining the operative procedures to be carried out at the time of operation. The reasons for the clinical findings in this case are mentioned with the aim of emphasizing the importance of shoulder pain, jaundice, midline colicky pains, together with vomiting, distention and obstipation, in the diagnosis of the obscure case of the less dramatic type of ectopic pregnancy.

J. THORNWELL WITHERSPOON

Bellei, A.: A Case of Cervical Pregnancy, Clin. Ostet. **15:** 19, 1937.

A case of primary cervical pregnancy is reported, in which the clinical diagnosis of carcinoma of the cervix complicating pregnancy had been made but corrected by microscopic section. The incidence is rare since only 32 cases of this condition are reported in the literature.

AUGUST F. DARO

te Groen, L. J.: An Interesting Case of Tubal Pregnancy. South African M. J. **11:** 236, 1937.

The author describes a case in which ectopic pregnancy recurred repeatedly in a patient whom he had treated nonoperatively on two occasions. The patient had a left ruptured tubal pregnancy verified at operation in 1923. Two years later a similar episode, diagnosed as a right ruptured tubal pregnancy, was treated with rest, ice bag, fomentations, etc. The patient recovered after three weeks' hospital care. In the same year she experienced a similar episode diagnosed as a second ruptured ectopic pregnancy with nonoperative treatment; it took her seven weeks to recover. In 1930 a diagnostic curettage was performed for dysmenorrhea. Two months later this was followed by a normal intrauterine pregnancy. In 1931 she delivered a normal healthy baby per vias naturales. She subsequently had two more normal pregnancies.

On Jan. 30, 1937, she was admitted to the hospital with a right ruptured tubal pregnancy. Operation revealed the hemorrhage occurring from the fimbriated end, and the tube was as thick as a finger. About one inch from the uterus the tube became of normal thickness. The ovary was fibrotic. Both tube and ovary were removed.

F. L. ADAIR AND S. A. PEARL

Reid, Ronald: A Case of Abdominal Pregnancy, Brit. M. J. **1**: 1301, 1938.

A description is given of an abdominal pregnancy diagnosed by laparotomy in a previously normal woman, aged 31 years, para ii. The possibility in this case is that it started as an ectopic gestation in a Fallopian tube when at six weeks a tubal abortion occurred. The extravasated embryo retained enough of its old connections to survive and grow. Abdominal pain was the outstanding symptom, as well as signs of internal hemorrhage. Control of hemorrhage from the placental attachments at operation was effected by pressure of hot packs.

The literature and statistics are briefly reviewed.

F. L. Adair and S. A. Pearl

Guzman, Gazitua, and Valeuzuela: Two Cases of Intraligamentous Pregnancy at Term, Bol. Soc. chilena de obst. y ginec. **11**: 160, 1937.

The authors' first case was in a gravida iv who came into the hospital complaining of irregular vaginal bleeding and an enlarging abdomen. The admission diagnosis was ovarian cyst. X-ray examination revealed an almost full-term fetus. Abdominal pain was present and an expectant plan of treatment was followed. The pregnancy was considered intrauterine. After an appreciable length of time, a laparotomy was done because of the peculiarities present. An extrauterine dead fetus weighing 2,100 gm. and 48 cm. in length was found in an intraligamentous sac. The placental attachment necessitated a bilateral salpingectomy and hysterectomy. A urinary fistula developed due to severance of one ureter.

The second case was diagnosed fibromyoma of uterus because of age of patient (44), and a negative Friedman test. The placenta in this case was easily removed from the broad ligament. A dead fetus weighing 1,750 gm. and 44 cm. long was delivered. Drainage was instituted through the pouch of Douglas. Postoperative convalescence was normal.

Mario A. Castallo

Patrick, A.: Advanced Extra-Uterine Pregnancy, Brit. M. J. **1**: 1156, 1937.

The author reports a case of an advanced ectopic pregnancy in the ampullary portion of the Fallopian tube. No history of menstrual irregularities, usually seen in ectopic pregnancy, was obtained. The patient had been sterile for six years prior to this gestation. An emergency operation in the acute illness of this patient revealed the true nature of the pregnancy.

Rupture of ectopic pregnancies usually occurs at the eighth week and very few continue after twelve weeks. This pregnancy advanced to nearly five months.

F. L. Adair and S. A. Pearl

Ormazabal, Olga Moretta: Tubal Pregnancy of 4½ Months, Bol. Soc. chilena de obst. y ginec. **1**: 323, 1936.

The author could find no reference in the literature of a similar tubal pregnancy which had advanced so far before rupture occurred. The author claims that in her case the ovisac with placenta was found entirely surrounded by the Fallopian tube wall.

Mario A. Castallo

Vilalta, F. S.: Study of Retention of an Ectopic Pregnancy to Term, Rev. méd. cubana **49**: 1, 1938.

A case of full-term ectopic pregnancy is reported by Vilalta. The Friedman test was negative, hence was not helpful. A simple x-ray picture did not reveal the true state of affairs but a uterosalpingogram showed a normal uterine cavity of nonpregnant size, quite distinct from a full-term fetus which presented by the breech. The author operated and removed both the baby and the placenta. No difficulties were encountered. The patient made an excellent recovery.

J. P. Greenhill

Crichton, E. C.: Full-Time Ectopic Pregnancy, South African M. J. **11**: 229, 1937.

Three cases of ectopic pregnancy at or near term are reported. In Case 1 there was no history of vaginal bleeding or abdominal discomfort throughout gestation. An attempted medical induction revealed the absence of uterine contractions following the administration of pituitrin. This may be a useful test in the diagnosis of advanced ectopic pregnancy or other extrauterine tumors.

Case 2 was characterized by abdominal pain throughout pregnancy which was unwisely ignored. At operation a portion of placenta was left behind without drainage and caused no harm. Cases are on record in which the whole placenta was left in the abdomen and subsequent normal pregnancies occurred.

Case 3 is remarkable because the child up to term attained a weight of 9 pounds and, though macerated at operation, showed no serious deformity.

The vast majority of babies which develop outside the uterus are below the average weight and display more or less serious deformities.

F. L. Adair and S. A. Pearl

Lailey, W. W.: An Unusual Case of Extrauterine Pregnancy, Canad. M. A. J. **36**: 67, 1937.

The writer reports an ovarian pregnancy in a 35-year-old woman, para iii, gravida v. The patient had vaginal spotting for three months with increasing abdominal discomfort. Vaginal examination revealed the fetal head bulging into the vaginal vault. The cervix was not found until the patient was anesthetized.

On abdominal incision, a uterus the size of a three months' pregnancy was found and a thin-walled sac enclosing the extrauterine fetus.

To control the hemorrhage caused by the placental edge separating, the uterus, right tube, and ovary and as much of the sac wall as could be were resected. Treatment for shock and hemorrhage was given.

The ectopic pregnancy had developed to a state four or five weeks beyond term and survived. The implantation was apparently on the ovary. Mother and baby survived.

H. Close Hesseltine

Holtz, F.: The Etiology, Symptomatology and Treatment of Tubal Pregnancy, Acta obst. & gynec. Scandinav. **16**: 509, 1936.

In the Gynecological Clinic at Upsala, 111 cases of tubal pregnancy were treated during the years 1924 to 1934. In no less than 47 out of 97 married patients, five years or more had elapsed before conception took place, pointing to the occurrence of factors impeding conception in a large number of cases.

Follow-up of a large number of women with salpingo-oophoritis who had had conservative treatment, and of women with febrile abortions, showed that salpingitis does not lead to tubal pregnancy in any considerable number of cases, the cause being probably more frequently found in adhesions around the tubes caused by small intraperitoneal hemorrhages from the adnexa.

Signs of pregnancy were observed in 97 cases (87.4 per cent). Internal hemorrhage accompanied by symptoms of shock was present in 45 (40.5 per cent). In 91 cases (82 per cent), external hemorrhage was found, being sparse and dark colored in 76.

Operation seems to be indicated not only in cases showing internal hemorrhage with severe symptoms but also in other cases on account of the danger of tubal rupture, infection of hematocele, and risk of the other tube becoming incapable of performing its functions because of formation of adhesions.

Fifty-seven patients were followed up for at least three years. Of 51 patients with a capacity for conception who had not avoided conception, 9 (17.6 per cent) had an intrauterine pregnancy. Out of 9 patients on whom salpingostomy on the remaining tube was performed, 7 remained sterile and 2 developed another tubal pregnancy.

J. P. Greenhill

Items

American Board of Obstetrics and Gynecology

Application for admission to the Group A, May, 1939, Board examinations must be on file in the Secretary's Office not later than March 15, 1939.

The general oral, clinical and pathological examinations for all candidates, Part II examinations will be held as follows: Group A, Saturday and Sunday, May 13 and 14; Group B, Monday and Tuesday, May 15 and 16, immediately prior to the Annual Meeting of the American Medical Association, at St. Louis, Missouri. Notice of time and place of these examinations will be forwarded to all candidates well in advance of the examination dates.

Candidates for re-examination in Part II (Groups A and B), must request such re-examination by writing the Secretary's Office before March 15, 1939. Candidates who are required to take re-examinations must do so before the expiration of three years from the date of their first examination.

The annual dinner meeting of the Board, to which all Diplomates and Candidates are invited, as well as wives and others interested in the work of the Board, will be held on Wednesday evening, May 17, following the close of the examinations.

The dinner meeting will be in the Tower Room of the Congress Hotel, St. Louis, at 7:00 P.M. (informal). Price $2.50 per plate. You may obtain tickets from Dr. Joseph L. Baer, 104 S. Michigan Ave., Chicago, Ill. Speaker: Dr. Robin C. Buerki, Director, Commission on Graduate Medical Education of the Advisory Board for Medical Specialties; topic: "The Value of Certification."

Application blanks and booklets of information may be obtained from Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Royal College of Obstetricians and Gynecologists

It is of interest to note that by Royal Command the title of "Royal" has been granted by H. M. the King to the British College of Obstetricians and Gynecologists. This action may be regarded as setting the seal of approval upon an institution which has occupied a position of increasing importance in English medicine. The membership of the College is at present over 600 and a diploma is issued only to those qualified by a long period of resident training in the specialty and after adequate examinations.